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The Journal of the British Paediatric Association

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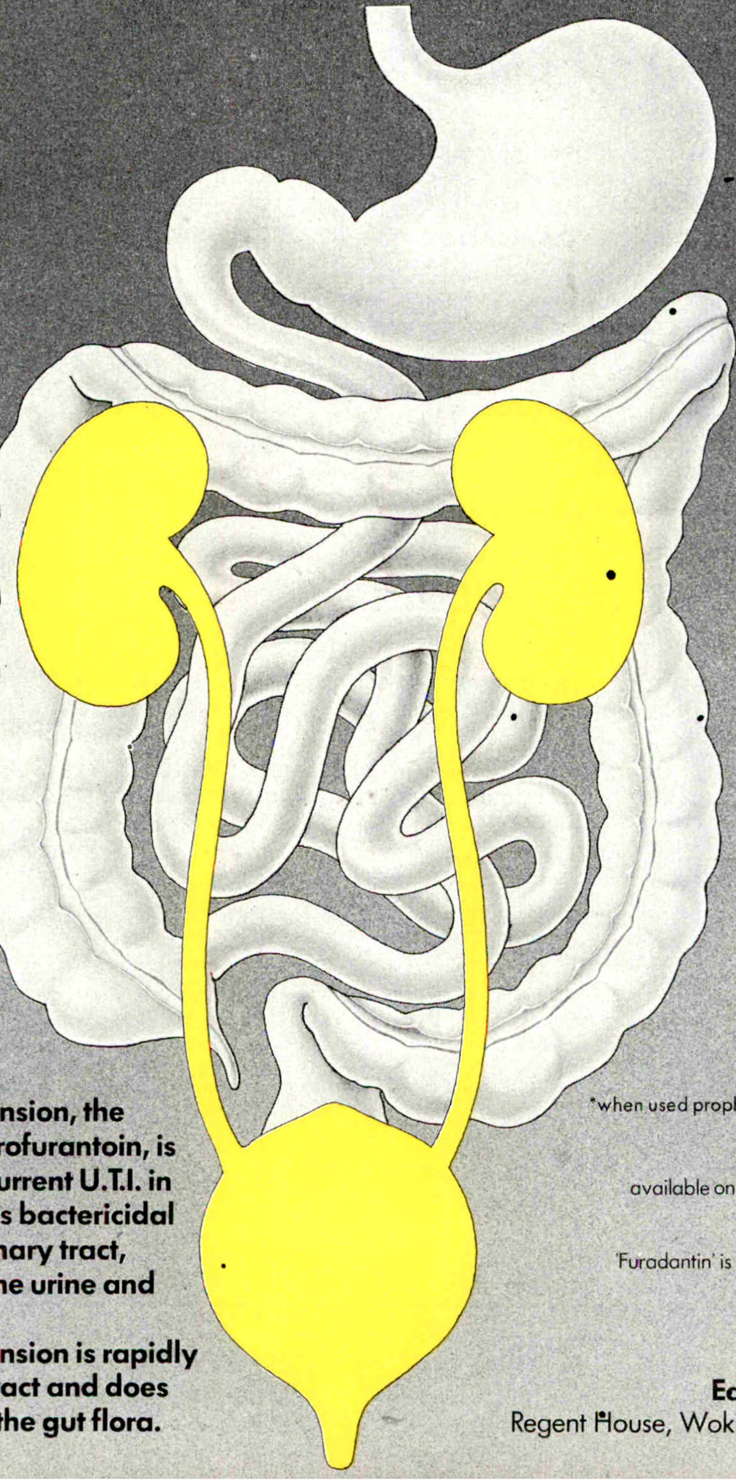

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Intellectual performance in children after circulatory arrest with profound hypothermia in infancy

D. F. DICKINSON AND J. E. SAMBROOKS

Royal Liverpool Children's Hospital

SUMMARY 38 children were assessed 22 months to 6 years after open heart surgery using circulatory arrest with deep hypothermia. The mean IQ of the group was 99·2 (SD 19·5). No correlation was found between IQ and the age or weight at operation or the duration of circulatory arrest. The results suggest that the technique gives effective protection to the brain during periods of circulatory arrest for up to 60 minutes.

Surgical treatment in early infancy is sometimes necessary in children with congenital heart disease either because of intractable cardiac failure or arterial hypoxia. The combined mortality from early palliation followed by later total correction led to attempts at complete correction as a primary procedure. However, early experience with standard cardiopulmonary bypass in infancy was associated with major problems in most centres (Baffes, 1968; Ching *et al.*, 1971; Hallman and Cooley, 1971) and although cardiopulmonary bypass has now successfully been used (Sugimura and Starr, 1977), many centres continue to use deep hypothermia with circulatory arrest for these patients. The technique offers the surgeon almost ideal operating conditions in an empty, still, and bloodless heart and several successful series of complete repairs of complex malformations have been reported (Mori *et al.*, 1972; Barratt-Boyes, 1973; Venugopal *et al.*, 1973).

The vulnerability of the developing brain to a number of insults has been well documented (Dobbing, 1974) and concern has existed regarding the long-term intellectual development of children subjected to periods of circulatory arrest in infancy. Although reports of neurological damage (Bjork and Hultquist, 1962) severely curtailed the use of deep hypothermia in the early 1960s, the incidence of serious neurological complications in the infants reported by Mori *et al.* (1972) was low, and subsequent reports have suggested that in the longer term, intellectual function remains within the normal range in most cases (Brunberg *et al.*, 1974; Stevenson *et al.*, 1974; Messmer *et al.*, 1976; Haka-Ikse *et al.*, 1978). Nevertheless, in each series abnormal neurological behaviour in the immediate postoperative period and later intellectual retardation was seen in a significant number of patients and further evaluation of the technique is needed.

Patients and methods

Between January 1971 and December 1975, 84 children underwent surgical correction of congenital heart disease at the Royal Liverpool Children's Hospital using deep hypothermia (core cooling) with circulatory arrest. During the period this technique was used, with few exceptions, for all children requiring open heart surgery at <2 years of age, or below 10 kg in weight. There were 29 deaths in hospital and one death later. One child has been lost to follow-up. Four children subsequently required a 2nd operation which was carried out under hypothermic conditions in 3 and using standard cardiopulmonary bypass in the 4th.

Assessment of intellectual ability was made by one of us (J.E.S.) in 38 of the 54 long-term survivors, 22 months to 6 years after operation. At the time of testing, the ages of the children ranged from 28 to 105 months (median 50). The children were those attending the hospital for a routine outpatient visit during 1976 and 1977 and those living in the immediate vicinity of Liverpool. No child was excluded because of a neurological abnormality noted before the operation. An informal interview with the parent(s) was followed by assessment of the child on one of four tests selected according to the age and ability of the child. The Wechsler preschool and primary scale of intelligence or the Wechsler

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J. E. SAMBROOKS, senior clinical psychologist

intelligence scale for children was used in 14 children and the Merrill Palmer scale of mental tests in 23. One severely handicapped child was assessed using the Griffiths developmental scale. In addition, all the children were assessed on the Vineland scale of social maturity.

The cardiac lesions of the tested children are given in Table 1. At time of operation the median age of the children was 9 months (range 5 days to 36 months), the mean weight 6·5 kg (range 2·4 to 12·3), and the mean duration of circulatory arrest 47 min (range 20 to 69). Hypothermia from 14 to 25°C (nasopharyngeal) was used, most children being arrested at 18 or 19°C. In these respects there were no significant differences between the tested group, the group of survivors as a whole, or the 29 children who did not survive.

Surgical technique. The surgical technique was described in detail previously (Hamilton *et al.*, 1973).

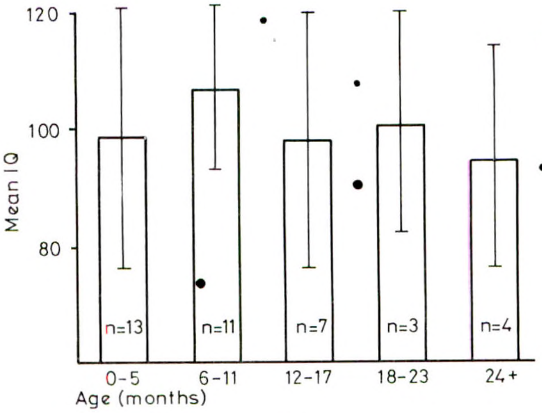
After induction of anaesthesia, lines for the continuous monitoring of arterial and central venous pressure are established. The electrocardiograph, nasopharyngeal, and oesophageal temperatures are also monitored continuously during the procedure. Cardiopulmonary bypass is established using a single right atrial cannula with pump return to the ascending aorta. A period of perfusion at 2·4 l/m^2 with the Temptrol infant model oxygenator (Bentley Laboratories Inc., USA) in conjunction with an infant heat exchanger, is used to maintain the rate of cooling between 0·5 and 1·0°C/min. After reaching a predetermined low temperature (usually 18°C) perfusion is continued for a further 5 minutes to allow for temperature equilibration within the body. The infant is then exsanguinated through the venous line, snares are applied to the venae cavae, and a single clamp is applied to the aorta and pulmonary artery to lessen the risk of air embolism. After repair of the cardiac lesion is complete, perfusion is re-established and rewarming is begun. Acidosis is corrected at 32°C and inotropic drugs used if necessary to support the circulation.

Results

The mean IQ of the 38 tested children was 99·2 (SD 19·5). On the Vineland scale of social maturity the mean score was 112 (SD 19). There was no significant difference in mean IQ between those patients tested using the Merrill Palmer scale of mental tests, and those tested using either the Wechsler intelligence scale for children or the Wechsler preschool and primary scale of intelligence. Although the number of patients in some groups is small, no statistically significant correlation was found between IQ and age at operation (Fig. 1), weight at operation (Fig. 2), and duration of circulatory arrest (Fig. 3). Children with cyanotic congenital cardiac lesions (mean IQ 99) did not score significantly lower than those with acyanotic lesions (mean IQ 99·7), and there was no significant

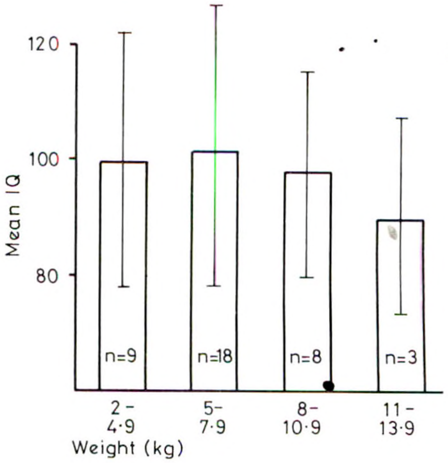
Table 1 *Cardiac lesions of tested children*

Transposition of great vessels	13
Ventricular septal defect	10
Total anomalous pulmonary venous drainage	7
Fallot's tetralogy	5
Pulmonary stenosis	1
Common atrioventricular canal	1
Aortic pulmonary window	1



Brackets indicate ± 1 SD.

Fig. 1 *Mean IQ plotted against age at operation.*



Brackets indicate ± 1 SD.

Fig. 2 *Mean IQ plotted against weight at operation.*

difference in mean IQ between the four main diagnostic categories (Fig. 4).

Seven (18%) children had IQ scores of at least 1 SD below the mean of the test (Table 2). Three were patients known to have neurological abnormalities dating from before the time of operation. Low cardiac output, with convulsions on the 4th post-operative day may have contributed to brain damage in one child, and one child (Case 6, Table 2) underwent 2 operations at an age at which we would now consider this technique to be inappropriate. A 6th child was uncooperative during testing. She attends a normal primary school and may well come within the normal range on retesting. No satisfactory explanation for retardation was found in the 7th child. One other child developed abnormal neurological signs in the postoperative period, but now has an IQ of 86 and a social quotient of 105 and attends a normal school.

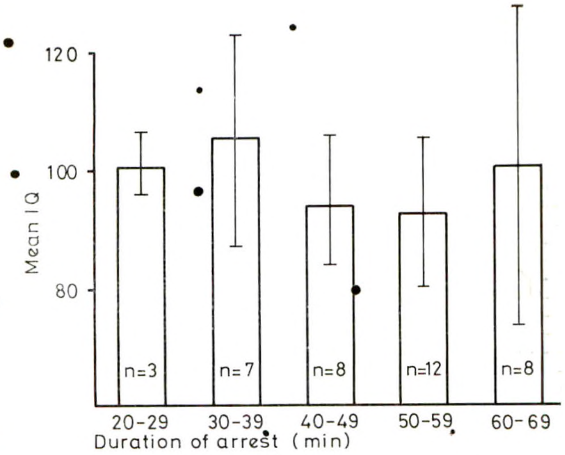


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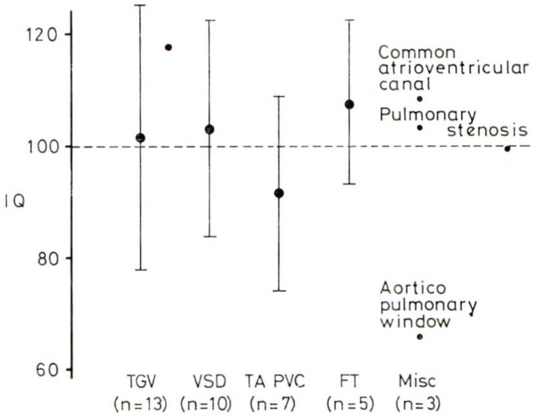
Fig. 3 *Mean IQ plotted against duration of circulatory arrest.*



Brackets indicate ± 1 SD.

TGV	Transposition of great vessels
VSD	Ventricular septal defect
TAPVC	Total anomalous pulmonary venous connection
FT	Fallot's tetralogy

Fig. 4 *IQ in relation to type of cardiac defect*

Most children assessed using Wechsler tests showed good correlation between verbal and performance scores. In 3 children however, an abnormal discrepancy was present, the performance score being significantly higher in 2 and the verbal score higher in the 3rd.

Discussion

The results of experiments in laboratory animals have shown that oxygen consumption and cerebral

Table 2 *Operation details of children scoring 1 SD below the test mean*

Case no.	*Cardiac lesion*	*At operation*		*Duration of arrest (min)*	*Temperature of arrest (°C)*	*IQ*	*Comments*
		Age (months)	*Weight (kg)*				
1	TGV	3	5·0	69	15	52	Cardiac arrest during catheterisation. Convulsions before and after operation.
2	TAPVD	1	2·7	50	20	76	Klippel Feil syndrome. Cardiac arrest in first month of life. Hypertonic before operation.
3	APW	2	2·4	50	25	65	Breech delivery. Severe birth asphyxia. Convulsions before operation. Hypertonic before operation.
4	TGV	25	7·9	63	18	76	Uncooperative during testing.
5	VSD	13	7·4	57	18	62	
6	TGV	34 (36)	11·3 (11·5)	57 (37)	19 (18)	74	Reoperation for pulmonary venous obstruction.
7	TAPVD	10	8·0	33	16	76	Low cardiac output syndrome for 48 hours after operation. Convulsions at 4 days after operation.

TGV = transposition of great vessels; VSD = ventricular septal defect; TAPVD = total anomalous pulmonary venous drainage; APW = aortico pulmonary window.

metabolic rate decrease at between 6 and 15%/°C fall in brain temperature (Rosomoff and Holladay, 1954; Hägerdal *et al.*, 1975). Within the range of hypothermia usually used in cardiac surgery at present, the relationship between cerebral oxygen consumption and temperature is probably linear. With this information, the safe period of circulatory arrest at between 16 and 19°C has been extended to between 60 and 75 min (Barratt-Boyes, 1973) and arrest periods of up to 120 min at 10°C have been reported (Belsey *et al.*, 1968). The possibility of neurological damage or intellectual impairment resulting from prolonged circulatory arrest or deep hypothermia has been appreciated for many years. Bjork and Hultquist (1962) reported 5 cases of fatal brain damage in children after hypothermic circulatory arrest. Histologic study of the brains in these patients showed a reduction in the number of ganglion cells in the globus pallidum with similar changes in the parietal cortex, hippocampus, and thalamus. Refinements in technique led by the University of Washington (Mohri *et al.*, 1969) and the University of Kyoto (Hikasa *et al.*, 1967) have enabled surgeons to operate safely in small infants with few major neurological complications.

Most centres have favoured the use of surface cooling to induce hypothermia, but metabolic studies of both surface-cooled and core-cooled patients have failed to establish conclusively the superiority of either technique (Harris, 1973). The advantages of core rewarming are widely accepted (Mori *et al.*, 1972; Barratt-Boyes *et al.*, 1973). Since 1970 we have used a technique of core cooling and core rewarming with a low incidence of cerebral problems. Although the mortality in the earliest years of the period was high, during 1973–77 the mortality rate was 22% in 102 patients under one year of age (Di Eusanio *et al.*, 1979).

Our results show no significant difference between the mean IQ of the survivors of hypothermic circulatory arrest and the mean of the normal population. The results compare favourably with the mean IQ previously reported in children with congenital heart disease who had not undergone corrective surgery (Linde *et al.*, 1967; Silbert *et al.*, 1969). Similar results have also been reported in a group of children who underwent corrective surgery at <2 years using conventional cardiopulmonary bypass (Sunderland *et al.*, 1973). Although these results are encouraging, in our series the range of intelligence within the tested group shows a wider dispersion about the mean than would be expected in a normal population, and a significant proportion of the survivors showed evidence of intellectual retardation. However, in 3 children, there was clear evidence before operation of neurological dysfunction of sufficient severity to explain their present disability (Table 2). If these patients are excluded the mean IQ of the group is 102 (SD + 17) and does not differ significantly from the distribution of intelligence within the normal population.

Laboratory studies of many animal species have shown that the immature animal is more tolerant of the effects of acute hypoxia than the adult (Dawes, 1968). In man, brain growth is known to continue to age 18 months (Dobbing, 1974) and the neonate might therefore be expected to show greater tolerance to a given period of circulatory arrest than the more mature child. The possibility that increasing age at the time of operation might be associated with a lower rate IQ score was suggested by Messmer *et al.* (1976). Our results show a similar tendency but the number of children >age 18 months at the time of operation is small and the correlation is not statistically significant. Nevertheless, the occurrence of mental retardation in 2 of the 4 patients who underwent operation at >2 years of age suggests that particular caution is needed if the technique is to be used at this age. Our current policy (Di Eusanio *et al.*, 1979) is to use this technique only in a few selected cases at age >12 months.

Neurological sequelae after circulatory arrest with hypothermia include convulsions, paresis, hypotonia, rigidity, choreoathetosis, alteration of consciousness or personality, and impairment of intellect (Björk and Hultquist, 1962; Mohri *et al.*, 1969; Mori *et al.*, 1972; Venugopal *et al.*, 1973; Brunberg *et al.*, 1974). Similar complications have been described after operation using conventional cardiopulmonary bypass (Gilman, 1965; Javid *et al.*, 1969). Many factors may be responsible for such neurological damage. Cardiopulmonary bypass, used both for cooling and rewarming may be complicated by embolisation of gas, fat, or fibrin-platelet aggregates (Aguilar *et al.*, 1971). Regional impairment of cerebral microvascular perfusion has been shown in experimental animals during core cooling and rewarming, and may be a factor in creating uneven cerebral cooling (Aoyagi *et al.*, 1975). Rapid core cooling may allow excessive temperature gradients to develop between blood and cerebral tissue and we take considerable care to control the rate of cooling (Di Eusanio *et al.*, 1979). Since cerebral blood flow is influenced by changes in arterial P_{CO_2} (Lassen, 1974), carbon dioxide concentrations of 10% are used in the inspired gas mixture below 30°C to promote cerebral vasodilatation during cooling. Accumulation of cerebral metabolites during prolonged circulatory arrest could also be a factor in the production of postoperative cerebral damage. However, if this were the case, it might be expected that longer periods of arrest would be associated with poorer intellectual function in the survivors. Our results do not support this conclusion, and suggest that the technique gives effective protection to the brain for periods of up to 60 min of circulatory arrest, and possibly for up to 70 min.

Previous authors (Linde *et al.*, 1967; Silbert *et al.*, 1969) have noted the tendency for older children with cyanotic congenital heart disease to have significantly lower IQ scores than children with acyanotic congenital heart disease. From their results, Silbert *et al.* (1969) came to the tentative conclusion that chronic hypoxia in the first 2 years of life might, by itself, have direct adverse effects on sensorimotor development, irrespective of any effect resulting from the reduced exercise tolerance of the cyanotic child. Linde *et al.* (1967), on the other hand, suggested that physical incapacity in the young child with cyanosis was the most important factor in the observed lower scores, and that this deficit in gross motor performance might result in an underestimation of the potential intellectual performance at a later age. In the present series defects were corrected, in all but 4 cases, before age 2 years and no significant difference in IQ was seen between the two groups. The possibility of psychological benefit resulting from early correction, although unlikely ever to be a major consideration in the timing of surgery, should not be discounted.

Detailed developmental assessment was not performed before operation and, indeed, many of the patients were sufficiently ill at that time for such testing to be of doubtful predictive value. We were unable therefore to use the patients as their own controls. Nevertheless, the distribution of intelligence within the tested group closely resembles that of the normal population, and suggests that the technique is effective in protecting the brain during prolonged periods of circulatory arrest.

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Congenital complete heart block in the newborn associated with maternal systemic lupus erythematosus and other connective tissue disorders

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SUMMARY Four babies with complete heart block associated with maternal systemic lupus erythematosus (SLE) are described, together with a 5th baby whose mother had serological abnormalities only. One baby had a rapidly fatal outcome, one has required digoxin for heart failure, and the remaining 3 are asymptomatic but remain in complete heart block. Additional manifestations were present in 2 of them. The spectrum of neonatal abnormalities that may occur in association with maternal SLE and related connective tissue disorders is discussed, together with the possible causes and the prognosis. We conclude that congenital heart block is more common than had previously been appreciated.

Congenital complete heart block, sometimes presenting with bradycardia before birth (Sankey, 1948), is a rare clinical entity present in about one in 20 000 live births (Michaelsson and Engle, 1972). Familial occurrence has been reported a number of times since the first description by Morquio (1901).

In about 30% of cases there is another congenital abnormality (Michaelsson and Engle, 1972) the most common of which is corrected transposition of the great arteries (Walker *et al.*, 1958), but an association with other congenital anomalies has been reported (Nadas and Fyler, 1972).

Of those cases with no associated abnormality some probably result from abnormal development of the embryonic conducting system (Lev, 1972). It is possible that others result from disruption of the conducting system by some inflammatory process *in utero* (Carter *et al.*, 1974), and there have been reports of an association between congenital complete heart block in the newborn and SLE in the mother. We can find only one report in the UK (Hull *et al.*, 1966), but we believe it is more common here than generally appreciated and we wish to report a further 5 cases, with survival in 4, to show that this is part of a spectrum of abnormalities which may be associated with maternal connective tissue disease.

Patients

Case 1. A boy born by vertex delivery at 31 weeks' gestation weighing 1·9 kg (1972). He was grossly hydropic with respiratory distress and cyanosis. The heart rate was extremely slow at 50/min. There was hepatosplenomegaly. The ECG showed complete heart block with an atrial rate of 150/min and a ventricular rate of 54/min. Despite supportive therapy he died at 36 hours. Unfortunately no detailed postmortem examination was performed.

Maternal history

The child's mother, born 1942, became extremely ill at age 21 with pericarditis, pleurisy, anaemia, arthralgia in the small joints of the hands, and episodes of paroxysmal tachycardia. Investigations at that time included a differential agglutination titre (DAT) for rheumatoid factor, positive at over 2560.

After delivery of the baby, the advice of one of us (V.W.) was sought and further investigation led to the maternal condition being diagnosed as SLE.

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The laboratory findings included an ESR of 120 mm in the 1st hour; gross hypergammaglobulinaemia (6·6 g/100 ml); antinuclear factor (ANF) positive at 1:50 titre, and the DAT and latex fixation tests strongly positive, but an LE cell test was negative.

***Case 2.** A girl, born by assisted breech delivery at 40½ weeks' gestation weighing 2·73 kg (9.11.76). Bradycardia, which had been present from 2 months before delivery, persisted at birth, heart rate 72/min. There was no cyanosis, oedema, cardiomegaly, or murmurs. The liver was palpable 3 cm and spleen 2 cm below the costal margin. There were many circular, pale, somewhat atrophic, depressed lesions of about 1 cm diameter, some surrounded by an erythematosus circle predominantly on the face lateral and superior to the eyes (Figure), but also some lesions on the scalp, neck, and chest.

The skin lesions faded at age 2 weeks but subsequently became more florid and extensive, extending down the trunk and abdomen with one lesion on the thigh. The lesions tended to diminish and extend, but at age 3 months all that remained were a few small scarred slightly telangiectatic lesions that were hardly noticeable with some petechiae predominantly on the face. The spleen was impalpable after age 8 months. Her weight is now on the 3rd centile, but she appears to be well and is developmentally normal. She remains in complete heart block.

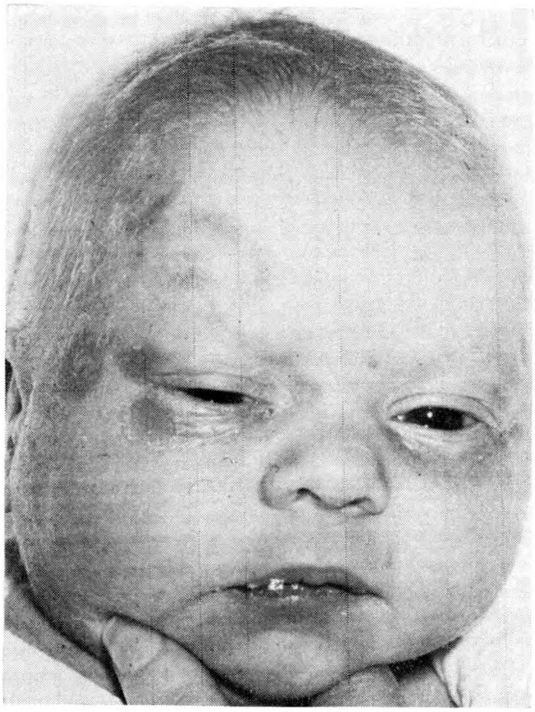

Figure *Case 2. Aged 3 days.*

Maternal history
The child's mother has suffered from SLE for 8 years manifested by lesions on the fingers and toes in the winter and discoid lesions on the face and chest in the summer. There has been no renal involvement and her general health has been good. Systemic corticosteroids or immunosuppressants have not been prescribed.

Previous pregnancies. Termination of pregnancy on social and medical grounds in 1972. Healthy baby boy weighing 2·875 kg born 1975 at 39½ weeks' gestation.

Investigations and diagnosis
The maternal diagnosis of SLE was made on the clinical and laboratory findings. Laboratory findings included a positive ANF with a speckled pattern of fluorescence on several occasions to a titre of 1 in 80; LE cells on 3 occasions: anti-DNA antibodies up to 103 units/ml (upper limit of normal 20); elutable nuclear antigen (ENA) positive at 1 in 64; Rose Waaler (RW) titre 1 in 80; total WBC frequently below 4×10^9/l (4000/mm^3). A skin biopsy from the foot showed a pronounced perivascular lymphocytic infiltrate with swelling of capillary endothelial cells.

No laboratory evidence for SLE was found in the baby apart from a weakly positive antinuclear antibody (ANA) test at 2 months. During the neonatal period simultaneous investigation of the baby and her mother included: full blood count, DNA binding, LE cells, RW test, immunoglobulins, and C3 and C4 component of complement. None was significantly abnormal in either. Neutropenia was found on one occasion at age 3 months in the baby (neutrophil count $0·95 \times 10^9$/l; 0·095/mm^3). ENA 3 months after delivery was positive in a titre of 1:64 in the mother but negative in the baby.

ECGs show complete heart block with an atrial rate of 130/min and a ventricular rate of 70 to 80/min. Chest *x*-rays showed a normal sized heart and normal pulmonary vasculature.

Case 3. A boy, born by caesarean section at term weighing 3·45 kg (10.1.77). Bradycardia, discovered shortly before delivery, persisted at birth with a heart rate of 60/min. His pulses were of good volume. There was a short grade 1 ejection systolic murmur audible in the pulmonary area and down the left sternal edge. There was no cyanosis and no oedema. Otherwise examination was negative and his general condition was good.

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*This case was reported in *Clinical and Experimental Dermatology* (Rendall and Wilkinson, 1978) with emphasis on the dermatological aspects.

An ECG showed a rate of 60/min with complete heart block. The chest *x*-ray showed slight cardiac enlargement with normal lung fields. At 4 months when his heart rate was 58/min he was in mild heart failure and put on digoxin. He has remained well since.

Maternal history

The child's mother since age 24 has suffered from joint pains and stiffness, dryness and grittiness of the eyes, chilblains, and white hands in the cold. Her symptoms are ameliorated with prednisolone. The diagnosis of SLE and Sjogren's syndrome were made on the history together with a positive latex fixation, RW test, and ANF positive to a titre of 1:500 with a homogenous pattern and a DNA binding of 75% (control 21%).

Previous pregnancies. Therapeutic abortion aged 21 years.

Case 4. A girl, weight 2·23 kg, was delivered normally at 38 weeks to a 34-year-old Jamaican in whom pregnancy had been complicated by persistent anaemia and an antepartum haemorrhage. The fetal heart was irregular during the last trimester. The child was noted to have a pulse rate of 60/min at birth. On examination she appeared to be otherwise normal and healthy although there was a short systolic murmur audible at the apex, and signs of very mild cardiac failure. An ECG confirmed congenital complete heart block, with a ventricular rate of 40/min, an atrial rate of 150/min, and narrow QRS complexes. There were also several brief episodes of ventricular tachycardia during the first 24 hours of life. The chest *x*-ray showed cardiomegaly. An echocardiogram was normal, as was the arterial oxygen tension in 100% inspired oxygen.

It transpired that the mother had suffered for a number of years with joint pains, rashes, and anaemia. Her ANF was positive in 1974 and again after the birth of the baby. The child's ANF was positive on day 3 but no skin lesions or haematological abnormalities were found. The cardiac failure settled rapidly without specific treatment. At 7 days the child was well and thriving although the systolic murmur and cardiomegaly remained. At 3 months the child remains well and there would appear to be no associated anomaly.

Case 5. A girl, born by vertex delivery at term weighing 2·48 kg (9.3.77). Fetal bradycardia was noted at 38 weeks' gestation, and at birth the heart rate varied between 56 and 60/min. On examination she appeared otherwise healthy and normal. An ECG showed complete heart block with an atrial rate of about 160/min, and a ventricular rate of 56 to 60/min. The chest *x*-ray was normal. She is asymptomatic and growing normally.

Maternal history

The child's mother, aged 35, has no symptoms suggestive of a connective tissue disorder, but has a weakly positive ANF of 1:10 and a positive rheumatoid factor of 1:64.

Previous pregnancies. A girl, born in 1971, completely normal and healthy.

Clinical and laboratory findings

The clinical and laboratory findings in Cases 1–5 are shown in the Table. The maternal diagnosis of SLE is indisputable in Cases 2 and 3 with the history plus the serological finding of raised DNA binding, and it is probable in Cases 1 and 4. Case 3 suffers also from Sjogren's syndrome. In Case 5 there are serological abnormalities only.

The 4 symptomatic mothers have all had symptoms for some years. There was an exacerbation of symptoms during pregnancy in the mother of Case 2. She had discoid skin lesions and so did her baby. On the whole the illnesses have been chronic and relatively mild with an absence of renal problems. Only in the mother of Case 3 were corticosteroids prescribed in the pregnancy. The mothers of Cases 1, 2, and 5 all had one normal baby each; the mothers of Cases 2 and 3 have each had one termination of pregnancy.

Four of the infants (Cases 2, 3, 4, and 5) are alive and well, although Case 3 required digoxin. Case 2 had discoid skin lesions and hepatosplenomegaly in addition to complete heart block. Case 1, who was hydropic at birth, also had hepatosplenomegaly. He was the only baby who died—on the 2nd day. Three of the 5 babies are small-for-dates (Cases 2, 4, and 5). Three are girls and 2 are boys.

Of the laboratory findings ANF is the only result to have been positive in all 5 mothers. It was also positive in the 2 babies (Cases 2 and 4) in whom it was tested.

Discussion

We have been able to find reports of 26 infants (of 20 mothers) with complete heart block associated with

Table *Clinical and laboratory findings in babies with complete heart block (Cases 1–5) and in their mothers*

Cases	*Sex*	*Weight (g)*	*Gestation (weeks)*	*Clinical condition of baby*	*Laboratory support for SLE in the baby*	*Maternal disease*	*Maternal support for SLE or other connective tissue disease*
1	M	1·97	31	1st pregnancy. Hydropic. Ventricular rate 54/min. Hepatosplenomegaly. Died 36 hours	No detailed necropsy. No investigations for SLE	SLE. Developed pericarditis, pleurisy, anaemia, fever, arthralgia 8 years before	ANF positive. DAT strongly positive
2	F	2·73	40½	3rd pregnancy. Ventricular rate 70/min. Discoid skin lesions Hepatosplenomegaly. Alive and well	Weakly positive ANA	SLE. 8-year history of discoid skin lesions, photosensitivity, chilblain-like lesions on hands and feet	ANA positive. LE cells. Raised DNA binding
3	M	3·45	40	2nd pregnancy. Ventricular rate 60–70/min. Heart failure at 4 months—digoxin started		SLE and Sjogren's syndrome. Pyrexia. Arthralgia, chilblains 4 years before	Latex fixation, RW, and ANF tests positive. Greatly raised DNA binding
4	F	2·23	38	Ventricular rate 40/min. Brief episodes of ventricular tachycardia. Alive and well	Positive ANF	Joint pains, rashes, and anaemia for several years	ANF positive
5	F	2·48	40	2nd pregnancy. Ventricular rate 56–60/min. Alive and well		Asymptomatic	ANF weakly positive. RW positive

maternal connective tissue disease in addition to our 5 cases: Plant and Steven, 1945; Hogg, 1957 (1 case); Wright *et al.*, 1959 (3 siblings); Hull *et al.*, 1966 (1 case); Altenburger *et al.*, 1977 (1 case); Chameides *et al.*, 1977 (6 cases); and McCue *et al.*, 1977 (14 cases).

Five of the 20 mothers were asymptomatic and had serological abnormalities only. 13 of the remaining 15 mothers were diagnosed as suffering from SLE, one from rheumatoid arthritis (RA) (McCue *et al.*, 1977), and one from the syndrome of hypocomplementaemia with cutaneous vasculitis (Chameides *et al.*, 1977). Many had suffered from their illnesses for some years, and had had an exacerbation during pregnancy. There had been renal involvement in some mothers and 4 were reported to have died soon after pregnancy.

One mother had twins (McCue *et al.*, 1977), 3 mothers had 2 siblings (Chameides *et al.*, 1977; McCue *et al.*, 1977), and one mother had 3 siblings—all with complete heart blocks (Wright *et al.*, 1959). Many of the mothers had normal siblings, but there appears to have been a high abortion rate in the families. The 11 mothers described by McCue *et al.* (1977) had 14 infants with complete heart block, 14 normal infants, and 5 abortions between them. The mother described by Hull *et al.* (1966) had 2 normal children, followed by one with discoid skin lesions, and then one with complete heart block and hepatosplenomegaly who died.

In fact 8 out of the 26 infants have died, 4 in the early neonatal period, and 4 later in childhood. None of our 5 infants with complete heart block had any associated cardiac abnormality, but 6 of the reported cases had at least one. Patent ductus arteriosus was present in 3 cases and transposition of the great vessels in 2. Two of the reported cases had, in addition to the complete heart block, discoid skin lesions and hepatosplenomegaly. Most of the surviving infants enjoy good health. The oldest patient is 24 and has given birth to 2 healthy children (McCue *et al.*, 1977). The sex ratio of the 26 cases is 16 female to 10 male. The results of serological tests have been reported on very few of these infants. McCue *et al.* (1977) reported one infant with high titres of ANA and Chameides *et al.* (1977) reported an infant with a negative ANA test.

In the whole series (including our cases) 22 (71%) out of 31 have so far survived.

Spectrum of neonatal disease

In a review of congenital SLE, Vonderheid *et al.* (1976) did not accept that complete heart block was a manifestation. However, it appears to be relatively common. The 31 cases known to us are unlike the 19 cases of other neonatal diseases (McCuistion and Schoch, 1954; Dias *et al.*, 1958; Nathan and Snapper, 1958; Seip, 1960; Epstein and Litt, 1961; Johnson, 1963 (cited by Reed *et al.*, 1967); Jackson, 1964; Hull *et al.*, 1966; Reed *et al.*, 1967 (2 cases); Cruveiller *et al.*, 1970; Jones, 1971; Hontani *et al.*, 1971; Goldberg and Diamond, 1973; Weiner, 1973 (2 cases cited by Goldberg and Diamond, 1973; Vonderheid *et al.*, 1976); Soltani *et al.*, 1974; Vonderheid *et al.*, 1976 (2 cases)), and unlike the 4 cases in which the neonatal illness was diagnosed as SLE but in which there was no maternal illness suggestive of SLE, with abnormal serological tests in 2 (Nice, 1962; East and Lumpkin, 1969; Vonderheid *et al.*, 1976 (2 cases)).

We have arbitrarily classified the cases of neonatal SLE into 4 groups.

I Babies with complete heart block with or without other manifestations (31 cases; as described above).
II Babies in whom the only clinical manifestation is discoid skin lesions (13 cases).
III Babies with manifestations other than or in addition to discoid skin lesions—mainly haematological (6 cases).
IV Babies with presumed neonatal SLE in the absence of maternal clinical disease (4 cases).

The various manifestations that have been reported may occur singly or in combinations, and in families siblings may be normal or have the same or different manifestations as the index cases. For example, Reed *et al.* (1967) described a first-born baby with discoid skin lesions who has a 4th born sibling with discoid skin lesions and splenomegaly.

Overall discoid skin lesions were present in 22 (41%) out of 54 cases. Three (16%) cases (including our Case 2) had the combination of complete heart block, hepatosplenomegaly, and discoid skin lesions. Splenomegaly with or without hepatomegaly was present in 12 (22%) infants. Haematological abnormalities—anaemia, and or leucopenia, and or thrombocytopenia—occurred in 8 (15%) cases. The only other clinical manifestations that have been described are inflammatory lesions of the hands (Dias *et al.*, 1958) and valvular heart disease (East and Lumpkin, 1969). Most of the noncardiac lesions were transient, diminishing or disappearing in the early months of life.

Sex incidence. Altogether there are 19 males and 34 females, and one other the sex of which is unknown to us. Where weights and gestation are known 15 (60%) out of 26 are light-for-dates. The maternal connective tissue disorder has been SLE in most cases. As with the families of infants with complete heart block, some pregnancies have resulted in abortions, some in the birth of normal babies, and some in the birth of babies with the same or other manifestations of congenital SLE. In many families there are relatives with connective tissue disorders.

The most common positive laboratory findings in the mothers and babies have been the ANF, the LE cell test, and rheumatoid factors, but no consistent correlation has been found between the presence or absence of these and the clinical condition of the baby.

The pathogenesis of complete heart block and the other abnormalities described in some infants of mothers with SLE or related connective tissue disorders is unknown. There is certainly evidence of an increased familial incidence of SLE and of some of the serological abnormalities which may be associated with it. Apart from the studies already quoted (Reed *et al.*, 1967; McCue *et al.*, 1977), Larsson and Leonhardt (1959) found 4 instances of familial SLE and more than 40 of familial chronic discoid LE.

SLE has been described throughout childhood. Peterson *et al.* (1963) described skin lesions of SLE in a child as young as 18 months, and Fish *et al.* (1977) included a child of 2. It is therefore not unreasonable to conclude that in some instances SLE might occur *de novo* in the newborn and not as a direct result of the maternal illness. The case described by East and Lumpkin (1969) may be an example of this.

The transplacental passage of some maternal factors, probably IgG antibodies, is the most likely mechanism for most cases. The transient nature of some of the manifestations, such as discoid skin lesions, would strongly support this.

Beck *et al.* (1966) were able to show that ANA can cross the placenta and that it has a half-life of about 16 days in the infant. They also showed that ANA can be present in the infant in the absence of disease, and it is known that some babies suffer from disease with no ANA detected, e.g. the case of Hontani *et al.* (1971). It therefore seems unlikely that transplacental passage of ANA is the cause of transient neonatal SLE although some other undetected antibody may be responsible. The LE cell factor is not constantly present in mother and infant pairs. It can be present in the infant with no pathological effects (Bridge and Foley, 1954). Neither DNA nor RNA antibodies were found in our Case 2 nor were they found in the mother after delivery. However, platelet antibodies were shown in a mother and baby both with thrombocytopenia (Nathan and Snapper, 1958).

Presumably various antibodies are concerned in different manifestations of the neonatal disease, but we have been unable to detect what these are. None of the serological markers of connective tissue diseases has been shown actually to cause the neonatal disease. Widespread endocardial fibroelastosis has been the histological change seen in the babies who have come to necropsy (Hogg, 1957; Hull *et al.*, 1966; Chameides *et al.*, 1977). In a review of pathological studies of hearts with congenital complete heart block by serial sectioning, Carter *et al.* (1974) drew attention to a group of hearts where the atrioventricular conducting system was disrupted by a process of connective tissue degeneration. These changes were similar to those found by Hogg (1957) and Hull *et al.* (1966) in the children of mothers with SLE. It is therefore suggested that maternal autoantibodies may cross the placenta and cause degeneration of the fetal conducting system. This may happen in more than one pregnancy (Wright *et al.*, 1959). Further support for an antibody derived from the mother being involved in the pathogenesis of complete heart block in the baby comes from the known occasional occurrence of complete heart block in adults with SLE (Becker, 1965; Moffitt, 1965). Necropsies from several cases have shown damage and replacement of conductive tissue by connective tissue, similar to that seen in cases of congenital complete heart block. Similar changes have been described in adults with rheumatoid arthritis (Lev, 1972).

It is not surprising that there is more than one maternal connective tissue disorder associated with these neonatal syndromes as there is considerable serological and, to a lesser extent, clinical overlap. The asymptomatic mothers presumably carry the same antibodies noxious to the fetus as the symptomatic mothers (e.g. our Case 5).

The relatively mild clinical course and prolonged duration probably reflects the fact that the women least seriously afflicted by their connective tissue disorders will have the most babies. In our 5 cases there was no history of spontaneous abortion in other pregnancies although in the families described by McCue *et al.* (1977) there was an abortion rate of about 30% which is in agreement with other authors (McGee and Makowski, 1970). We note a high (60%) incidence of light-for-dates infants. However, in spite of this and the congenital abnormalities that may occur in some babies the prognosis for most liveborn infants is good.

The most serious manifestation is complete heart block. 22 (71%) out of 31 have survived. The management and prognosis of these children would not seem to differ very much from that of congenital complete heart block of any other cause. If the ventricular rate is more than 40 and the atrial rate is less than 140 and the QRS complex is narrow, the prognosis may be as good as 90% survival, half of the deaths occurring in the first year of life (Michaelsson and Engle, 1972).

Some mothers had some exacerbation of their symptoms during pregnancy—the skin lesions in the mother of our Case 2 were particularly severe during 2 pregnancies—and in a few the SLE only became apparent during pregnancy or in the postpartum period. Most authors who have studied SLE in pregnancy comment on the tendency to exacerbation of symptoms at this time (Dubois, 1966; McGee and Makowski, 1970). However, in spite of exacerbation of symptoms during pregnancy some of these mothers have had further pregnancies.

Conclusions

Congenital complete heart block is the most serious of a number of abnormalities that may be present in liveborn babies of mothers with connective tissue disorders. This possibility should be considered in the differential diagnosis of fetal bradycardia. When a baby is born with complete heart block, assessment of the mother may sometimes show a hitherto unsuspected connective tissue disorder. The association of heart block in the baby and connective tissue disorder in the mother is probably more common than had generally been appreciated.

Heart block is but one of a number of manifestations that may be present, and it appears that an intriguingly wide spectrum of disorders can occur in both the mother and her infant. A possible way of investigating this phenomenon would be to find what immunological differences there are in successive pregnancies of women who produce infants with different manifestations of congenital SLE.

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Tables of clinical and laboratory details of the other infants with congenital SLE can be obtained from the authors on request.

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Behavioural deviance in children with early treated phenylketonuria

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SUMMARY A sample of 99 early treated phenylketonuric children showed higher levels of behavioural deviance than 197 matched controls. For boys this excess of behavioural deviance persisted when IQ was taken into account. For phenylketonuric girls however it was restricted to those with IQs<70. The type of behavioural deviance shown by the boys over the whole IQ range was predominantly neurotic. The levels of behavioural deviance found in phenylketonuric children were among the highest that have been reported for children with various handicapping conditions.

It has now been shown that early treatment of phenylketonuria (PKU) results in a reasonably full preservation of intellectual functioning, although there may be a failure to reach full cognitive potential (Berman and Ford, 1970; Hudson *et al.*, 1970; Koch *et al.*, 1973; Smith and Wolff, 1974). The behaviour and emotional development of early treated children has been less thoroughly investigated (Wood *et al.*, 1967; Hackney *et al.*, 1968; Siegel *et al.*, 1968; Frankenburg *et al.*, 1973). These aspects of personality development are of importance in children with PKU because of the inevitable stresses that they are likely to meet as a result of their highly artificial diet. The capacity to cope with this diet will depend on the child's own adjustment to an increasing extent as he gets older. A girl with PKU is particularly likely to face stress in her child-bearing years because of the likelihood of her giving birth to a handicapped child. This risk to the fetus is probably reduced if a low phenylalanine diet is given during pregnancy, although the diet should be introduced before conception and no guarantee of a normal outcome can be given. Finally, because of the higher rates of psychiatric disorder in children with brain dysfunction (Graham and Rutter, 1968), even children in whom PKU is treated early may have an increased risk of disturbance, however strictly the diet is enforced, because blood phenylalanine levels are bound to vary over a wider range than in the normal child. For these reasons it was thought worthwhile to investigate behavioural deviance in children with PKU.

Patients and methods

Newborn infants in the UK are tested for raised blood phenylalanine levels between the 6th and 14th day of life. The Medical Research Council and the Department of Health and Social Security maintain, initially at Alder Hey Hospital, Liverpool, and currently at the Institute of Child Health, London, a phenylketonuria register. Paediatricians and screening laboratories are asked to notify newly diagnosed cases and at yearly intervals paediatricians are asked to provide follow-up details. The organisation of the register has been described by Hudson and Hawcroft (1977). Paediatricians are asked to arrange for IQs to be measured in all the children at 4 years (Stanford Binet) (Terman and Merrill, 1960), and then at 8, 10, and 12 years (Wechsler intelligence scale for children) (Wechsler, 1949), within 6 weeks of each child's birthday; the psychologist carrying out the test at 8 years is also asked to give a Schonell graded word reading test (Schonell, 1955).

Since 1972 paediatricians have been requested to ask parents to complete a behaviour questionnaire (Rutter A scale) of known reliability and validity

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(Rutter *et al.*, 1970b) when the child is 8 years old. At the same age, after obtaining parental permission, the child's class teacher is asked to complete a behaviour questionnaire (Rutter B scale) (Rutter, 1967) on the patient and, as controls, on 2 children in the same class of the same sex and nearest in age to the patient. The information on the control children is provided anonymously.

The Rutter parent and teacher scales consist of descriptions of behaviour rated as 'certainly applies', 'applies somewhat', and 'doesn't apply' (scored 2, 1, and 0 respectively). The teacher scale has 26 such items and the parent scale 18; the parent scale has, in addition, 13 items on health and habits (similarly scored 2, 1, and 0). Children scoring 9 or more on the teacher scale or 13 or more on the parent scale, have been shown by Rutter to have a higher risk of psychiatric disorder than those with lower scores. Furthermore, the deviant behaviour shown by children with high scores can be classified into 3 diagnostic types—antisocial, neurotic, or mixed—depending on the ratings of relevant individual items (Rutter *et al.*, 1970b). In the present study because numbers were small, antisocial and mixed groups are combined in the analysis.

The children in the present study are the first 99 children with early treated PKU on the register whose parents had completed a behaviour questionnaire. For 38 other early treated cases no parent behaviour questionnaire had been obtained. Teacher behaviour questionnaire data are also available for this sample and for their 197 matched control children (data were missing for one control child). IQ data were obtained for a subsample of 86 PKU children. Parent scale ratings and IQs were not obtained on control children.

Results

Overall rates of behavioural deviance on the teacher Rutter scale for patient and control groups. Table 1 shows the numbers of patient and control children that were identified by the teacher scale as being behaviourally deviant. More (40%) of the patient sample were behaviourally deviant than the control group (20%) ($\chi^2=13\cdot50$, df=1, $P<0\cdot001$). A greater proportion of the total patient sample (22%) showed neurotic deviance than did the control group (8%) ($Z=3\cdot59$, $P<0\cdot001$). The proportions in the 2 groups showing antisocial deviance were not significantly different.

There is a difference between the boys and girls in the patient sample. The male patients showed more frequent behavioural deviance than the controls ($\chi^2=21\cdot38$, df=1, $P<0\cdot001$) and the proportion of male patients with neurotic deviance (31%) was greater than that of the controls (4%) ($Z=2\cdot15$, $P<0\cdot05$); the proportion of male patients with antisocial deviance although twice that of the controls was not significantly different. For female patients neither the overall rate of deviance nor the rate of antisocial or neurotic deviance was significantly greater than for controls. The greater behavioural deviance among the children with PKU is due mainly to the neurotic deviance among the boys.

Parental Rutter scale rates of deviance for the patient group. The children with PKU showed the same pattern of deviance on the parental scale as was found on the teacher scale. The parents identified fewer children as deviant (24%) than the teachers (40%) ($\chi^2=5\cdot91$, df=1, $P<0\cdot02$) but, like the teachers, they more often identified neurotic deviance than antisocial deviance. On the parent scale boys (33%) again more often showed deviance than girls (17%) and although the rates of antisocial deviance were similar for boys (11%), and girls (7%), the parents identified more boys (22%) than girls (9%) as neurotic. None of these sex differences is however significant.

Table 1 *Rates of behavioural deviance on teacher Rutter scale in patients and controls*

	Not deviant	*Deviant*	*Type of deviance*		*Total*
			Antisocial and mixed	*Neurotic*	
	No. (%)	*No. (%)*	*No. (%)*	*No. (%)*	
Controls					
Total	157 (80)	40 (20)	25 (12)	15 (8)	197
Boys	74 (83)	15 (17)	11 (12)	4 (4)	89
Girls	83 (77)	25 (23)	14 (13)	11 (10)	108
Patients					
Total	59 (60)	40 (40)	18 (18)	22 (22)	99
Boys	20 (44)	25 (56)	11 (24)	14 (31)	45
Girls	39 (72)	15 (28)	7 (13)	8 (15)	54

Rates of behavioural deviance on teacher Rutter scale for children with different IQ levels within the patient group. The mean IQ at 8 years was for boys 89·74 (SD 19·33) and for girls 83·25 (SD 17·72). The product moment correlation between the total score on the teachers scale and IQ for boys was $-0\cdot29$ ($P<0\cdot05$) and for girls $-0\cdot42$ ($P<0\cdot01$).

Table 2 shows that the rates of behavioural deviance for the PKU children vary with IQ measured at 8 years. The IQs of the control children were not measured, so comparison was made between patients in each IQ group and controls undifferentiated as to IQ. PKU boys with IQs<70 show a greater incidence of behavioural deviance (66·7%) than controls (17%) ($\chi^2=9\cdot27$, df=1, $P<0\cdot01$) and are more likely, if deviant, to show neurotic deviance (Fisher's exact probability test $P=0\cdot03$). Patient boys with IQs in the range 70–99 again show more deviance (62%) than controls ($\chi^2=15\cdot88$, df=1, $P<0\cdot001$) but with no significant difference in the type of deviance. Those patient boys with above average IQs (IQ ⩾100) show more deviance (41·7%) than controls, although this difference is not significant. However those PKU boys with IQs>100, if deviant, are more likely than the controls to be neurotic (Fisher's exact probability test $P=0\cdot05$).

For the PKU girls with IQs<70 there is more behavioural deviance (75%) than in the control girls (23%) ($\chi^2=11\cdot86$, df=1, $P<0\cdot001$), but no significant difference in the type of deviance. PKU girls with IQs in the range 70–99 show no significant differences in the rates of deviance or type of deviance from the control girls. However, for PKU girls with average and above average IQs (IQ⩾100) there were no cases of behavioural deviance, compared with 23% for the control girls ($\chi^2=4\cdot21$, df=1, $P<0\cdot01$).

Discussion

The results of the study show that PKU children had significantly higher rates of behavioural deviance than matched controls. The high rate of deviance however is restricted to boys, and to girls with IQs<70. Previous work with the Rutter scales has demonstrated that behavioural deviance is closely related to the presence of psychiatric disorder, defined as a significantly handicapping behavioural or emotional disturbance (Rutter, 1967; Rutter *et al.*, 1970b). The high rate of deviance found among the PKU children of this study probably indicates that these children have a higher rate of psychiatric disorder than normal children. These findings are not in agreement with those of Siegel *et al.* (1968) who used an unstandardised school behaviour profile and compared PKU children with matched controls, finding no greater amount of behavioural deviance in 13 PKU children.

In the present study 20% of control children were rated as behaviourally deviant on the teacher questionnaire. This percentage is high compared with that found in the Isle of Wight (IOW) study (Table 3) but is almost identical with the figure of 19·1% found in a study of randomly selected 10-year-old children living in an inner London borough (Rutter *et al.*, 1975), which is probably representative of children living in big cities in the UK. We do not have data on the urban/rural distribution of the PKU children but it is likely that, as with the general population, most of them live in urban areas.

The rate of 40% deviance on the teacher questionnaire for the children with PKU is higher than any other group of children so far reported, except for IOW children suffering from combined lesions above the brain stem (usually cerebral palsy) with or without epilepsy (Table 3). The rate of 24% deviance

Table 2 *Rates of behavioural deviance on teacher Rutter scale for patients with different IQ levels*

Patients	*Not deviant*	*Deviant*	*Type of deviance*		*Total*
			Antisocial and mixed	*Neurotic*	
	No. (%)	*No. (%)*	*No. (%)*	*No. (%)*	
Boys					
IQ<70	3 (33)	6 (67)	1 (11)	5 (56)	9
70–99	8 (38)	13 (62)	9 (43)	4 (19)	21
⩾100	7 (58)	5 (42)	1 (8)	4 (33)	12
Girls					
IQ<70	3 (25)	9 (75)	6 (50)	3 (25)	12
70–99	19 (83)	4 (17)	1 (4)	3 (13)	23
⩾100	9 (100)	0 (0)	0 (0)	0 (0)	9

Table 3 *Rates of behavioural deviance in various populations and groups with a range of disorders*

Population/groups	*No.*	*Age (years)*	*% deviant on*	
			Teacher scale	*Parent scale*
PKU	99	8	40	24
PKU controls	197	8	20	—
IOW total population (Rutter *et al.*, 1970b)	2199	10–11	7·1	6·8
Inner London Borough total population (Rutter *et al.*, 1975)	1689	10	19·1	—
Asthma (Graham *et al.*, 1967)	65	9–11	10·7	10·5
Miscellaneous other physical disorders (Rutter *et al.*, 1970a)	127	10–12	12·6	9·6
Uncomplicated epilepsy (Rutter *et al.*, 1970a)	55	5–14	26·7	24·5
Lesions above brain stem (no fits) (Rutter *et al.*, 1970a)	22	5–14	41·7	23·8
Lesions above brain stem (fits) (Rutter *et al.*, 1970a)	12	5–14	38·5	30·0
Brain lesion (Seidel *et al.*, 1975)	33	5–14	30	—
Peripheral i.e. lesions not brain (Seidel *et al.*, 1975)	42	5–14	10	—

on the parent questionnaire is also similar in children with brain lesions and those with uncomplicated epilepsy and is again higher than all others reported. However the children in the present study were younger than those of other studies, and a previous study (Graham and Rutter, 1973) showed that younger children tend to have higher rates of deviance when measured by the Rutter scales.

Another factor which may have contributed to the high rates of deviance observed in children with PKU is their low IQs. Previous work with normal children has shown a relationship between IQ and behavioural deviance, particularly for the teacher scale. Children with intellectual retardation (IQ <70) on the IOW (Rutter *et al.*, 1970b) showed deviance rates of 41% with roughly equal proportions of neurotic and antisocial deviance, and children with psychiatric disorder have been shown to have slightly lower IQs than normal controls (Rutter *et al.*, 1970b); however the effect is slight (equivalent to about 5 IQ points), and for boys it is restricted to those with antisocial disorders. The high rate of deviance of PKU girls is confined to those with IQs<70, and boys with IQs<70 showed a particularly high rate of deviance. However boys with IQs>70 also showed significantly more frequent behavioural disturbance; this together with the high rate of neurotic disorder among the boys suggests that low IQs cannot be the only explanation for the behavioural deviance.

It is not possible from these data to find the cause for the high rate of behavioural deviance among PKU children, although there are several possibilities, namely: (1) direct effect of raised blood phenylalanine levels on brain cell metabolism producing disordered functioning, (2) effect of phenylalanine levels on brain growth and development in early life, (3) psychological effects of a very abnormal diet for a long period on the child himself or via its effect on family relationships (Keleske *et al.*, 1967; Sibinga and Friedman, 1971; Bentovim, 1976), and (4) a genetic mechanism linking the gene producing PKU with others producing a vulnerability to psychiatric disturbance. Psychiatric disturbance, which the high rate of behavioural deviance implies, is a handicap which the treated child (particularly boys) with PKU is more likely to show than children in the general population; those managing the condition may find it helpful to be aware of this fact.

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We wish to pay tribute to Dr F. Hudson who, until his death in 1976, was responsible for the running of the PKU register and whose enthusiasm and dedication are responsible for the register now providing a valuable research tool, which should allow much further work aimed at the improvement of the management of patients with PKU.

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Intestinal bile salts in cystic fibrosis

Studies in the patient and experimental animal

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SUMMARY The quantitative and qualitative distribution of bile salts in the duodenal juice of 13 patients with cystic fibrosis (CF) was studied after a test meal. The effects of triolein (TO), bovine serum albumin (BSA), and ricinoleic acid (RA) on the absorption of taurocholate (TCA) in the distal ileum of the rat *in vivo* was also studied.

The mean (and ranges) of total bile salt concentrations, glycine: taurine conjugate ratios, and percentage of dihydroxy bile salts in the patients with CF and pancreatic insufficiency were 3·5 (1·3–6·6) mmol/l, 8·6 (>10–3·1), and 37 (10–60) compared with control values of 7·4 (3·0–16·0) mmol/l, 3·0 (1·3–4·5), and 61 (52–70) respectively. The differences between the control and CF values were statistically significant ($P<0\cdot01$–$P<0\cdot001$). Three of the 13 CF patients had total bile salt concentrations <2 mmol/l, 8 had much higher glycine: taurine ratios, and 8 had a reduced percentage of dihydroxy bile salts. In 2 patients with normal pancreatic enzyme activities, duodenal bile salts were both quantitatively and qualitatively normal. TO (10 and 30 mmol/l), BSA (3%). and RA (5 mmol/l) had no inhibitory effect on the ileal absorption of TCA.

These results show pronounced abnormalities of duodenal juice bile salts in CF with pancreatic insufficiency consistent with a broken enterohepatic circulation (EHC); such abnormalities may contribute to defective lipid absorption in CF. The data in the experimental animal do not support the suggestion that unhydrolysed dietary substrates play a role in the pathophysiology of the broken EHC.

Recent studies have shown that children with cystic fibrosis (CF) excrete similar amounts of faecal bile salts as patients with ileal resections (Weber *et al.*, 1973, 1976; Goodchild *et al.*, 1975), and on the basis of kinetic studies, this increased faecal loss appears to be secondary to a broken enterohepatic circulation (EHC) of bile salts (Watkins *et al.*, 1974, 1977). The pathogenesis of the broken EHC has not been defined. Weber *et al.* (1973, 1976) reported a significant correlation between faecal fat and bile salt excretion, and found that pancreatic extracts and/or a low fat diet supplemented with medium-chain triglycerides markedly reduced the faecal excretion of bile salts. From these findings they suggested that unhydrolysed triglycerides might impair the ileal absorption of bile salts.

We investigated the total and individual bile salt patterns in the proximal small intestine of children with CF after a test meal, and studied some of the pathophysiological mechanisms that may be responsible for the broken EHC in the rat ileum.

Subjects and methods

Thirteen (6 boys and 7 girls) patients with CF were investigated, their ages varied from 1 to 182 months with a mean of 52·3 months. The diagnosis of CF was established by the finding of sweat Na and Cl concentrations of >70 mmol/l on at least two occasions in volumes of sweat >100 mg. All the patients had typical clinical features, and all except 2 had markedly reduced activities of pancreatic lipase, trypsin, amylase, and esterase compared with control values (McCollum *et al.*, 1977). Pancreatic extracts and antibiotics were discontinued 48 hours before administering the test meal. The control group (6

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boys and 4 girls) consisted of children with suspected malabsorption who were proved to be normal after extensive investigation; their ages ranged from 16 to 192 months with a mean of 40 months. None of the subjects had clinical or biochemical (serum proteins, bilirubin, and transaminases) evidence of liver disease.

Details of the test meal and duodenal intubation procedure have been described elsewhere (McCollum *et al.*, 1977). The meal, which was a modification of the Lundh meal, contained carbohydrate (4%) in the form of glucose, protein (4%) as comminuted chicken, and fat (4%) as corn oil; it was administered via a nasogastric tube after an overnight fast in the older children or after a 4-hour fast in young infants. Two-hour postprandial collections of juice were then obtained by siphonage on ice and aliquots of this postprandial pool were analysed.

Total bile salt concentrations in the duodenal aspirates were determined by the enzymatic procedure of Iwata and Yamasaki (1964) using 3-α-hydroxy steroid dehydrogenase (Cambrian Chemicals Ltd) after their extraction on Amberlite XAD-2 resin (Makino and Sjovall, 1972) supplied by British Drug Houses Chemicals Ltd. Individual bile salt concentrations were determined by the same method after separation on thin-layer chromatography using the solvent system of Hofmann (1964); amyl acetate/propionic acid/n-propanol/water (4:3:2:1 by vol). Both procedures gave consistent recoveries of >85%.

Animal experiments. The animal experiments were performed using an *in vivo* closed-loop model as previously described (Harries and Sladen, 1972; Sladen and Harries, 1972). A 20 cm segment of terminal ileum was used in male Wistar rats weighing 250–300 g after an overnight fast, water being allowed *ad libitum.*

All solutions were prepared on the day of the experiment. The solutions were mixed by ultrasound and gassed with 95% O_2 and 5% CO_2 to pH 7·1 immediately before instilling approximately 2 ml into the loop. The control solutions contained 10 mmol sodium taurocholate (TCA) (Koch Light)/l, 1 mmol oleate/l and 0·5 mmol monolein/l (Sigma Chemical Company Ltd), 4 mmol KC1/l, 25 mmol $NaHCO_3$/l, and were made up to 280 mosmol/l with NaCl. ^{14}C labelled taurocholate (Radiochemical Centre, Amersham) was added to give an activity of 1 μCi/ml. The test solutions were of a similar composition to the control solutions but, in addition, contained 10 or 30 mmol triolein (Sigma Chemical Company Ltd)/l, 3% bovine serum albumin (fraction V from Armour Chemical Company), or 5 mmol sodium ricinoleate (Eastman Chemical Company)/l. The stock lipid solutions were made up in organic solvents, and appropriate aliquots were evaporated to dryness under nitrogen before mixing with the bile salt-buffer solution.

After the absorptive period a 100 μl aliquot of the fluid remaining in the loop was counted in 10 ml of a dioxan-based scintillant: naphthalene 70 g, PPO 7 g, POPOP 0·0526 g/l dioxan (Hopkin and Williams Ltd). The solution was counted in a LKB Wallac beta counter with external standardisation.

Statistical analysis. The significance of differences between mean values was assessed by the Student's *t* test.

Results

Duodenal bile salts. Figs 1, 2, and 3 show the values for total bile salt concentrations, the molar ratios of glycine to taurine conjugates, and the percentage of dihydroxy bile salts in the duodenal juice of patients with CF and pancreatic insufficiency compared with controls. Unconjugated bile salts were not detected.

In the controls, the mean (and ranges) of total bile salt concentrations, glycine: taurine conjugate ratios, and percentage dihydroxy bile salts were

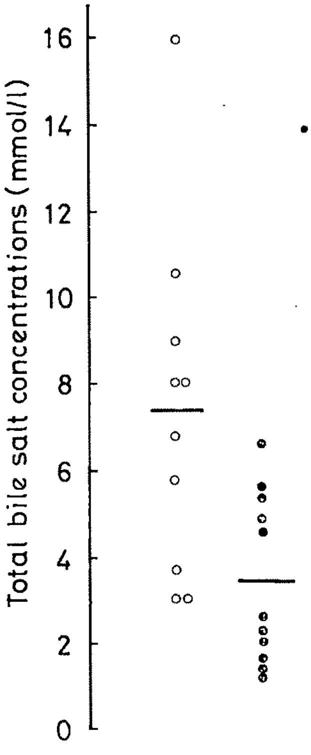


Fig. 1 *Total bile salt concentrations in duodenal juice of CF patients with pancreatic insufficiency.*

O=Controls;
●=CF patients.

7·4 (3·0–16·0) mmol/l, 3·0 (1·3–4·5), and 61 (52–70) respectively. Pronounced differences were found in the CF patients with pancreatic insufficiency, corresponding values being 3·5 (1·3–6·6) mmol/l, 8·6 (>10–3·1), and 37 (10–60); P values were <0·01, <0·001, and <0·001 respectively. Six of these 11 patients with CF had total bile salt concentrations that were below the control range, and in 3 of these the concentrations were less than the critical micellar concentration (i.e. 2 mmol/l). Eight of the 9 patients had markedly increased glycine to taurine conjugate ratios. In six the ratio was 10 or greater, taurine conjugates being undetectable or only present in trace amounts. In 8 of the 9 patients the percentage of dihydroxy bile salts was reduced, and 6 of these patients were less than one year old. There was no apparent relationship between total bile salt concentrations or glycine: taurine ratios and age.

In the 2 patients with normal pancreatic enzyme activities, duodenal bile salts were both quantitatively and qualitatively normal. The total bile salt concentrations were 16·1 and 25·5 mmol/l, the glycine: taurine ratios 4 and 3·5, and the percentage dihydroxy bile salts 56 and 70 respectively.

Animal studies. Preliminary experiments were performed in order to establish the relationship between TCA absorption and the absorptive period, and the results are shown in Fig. 4. Luminal disappearance of TCA was very rapid during the first 30 min. By 30 min the mean percentage absorption of TCA was 89% compared with 77% for the 20-min absorptive period. When expressed as μmol/g wet weight of ileum corresponding mean values for the 1-, 5-, 10-, 20-, 30-, and 40-min absorptive periods were 0·86, 5·77, 9·30, 10·41, 13·74, and 11·20

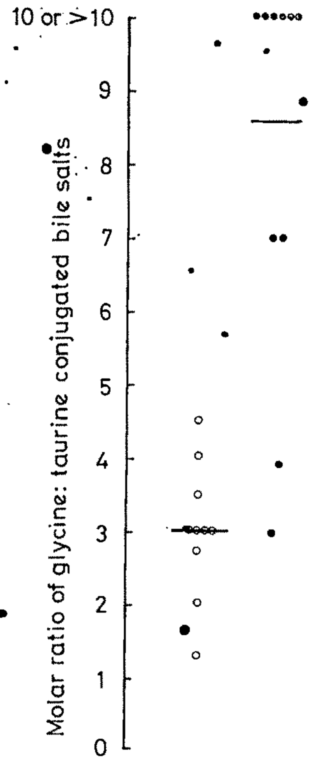


Fig. 2 *Molar ratio of glycine: taurine conjugated bile salts in duodenal juice of CF patients with pancreatic insufficiency.*

O = Controls;
● = CF patients.

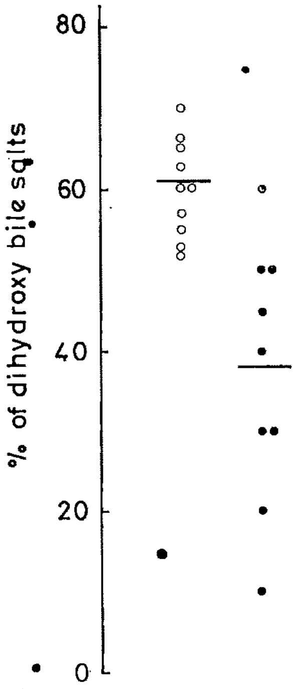
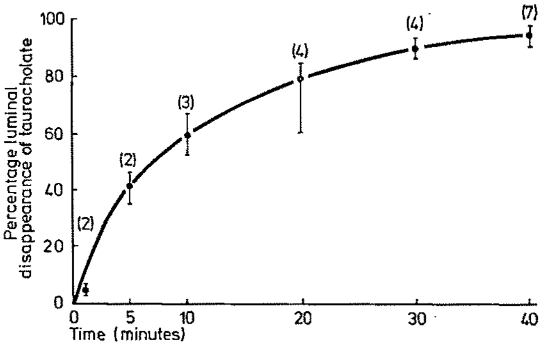


Fig. 3 *Percentage of dihydroxy bile salts in duodenal juice of CF patients with pancreatic insufficiency.*

O = Controls;
● = CF patients.



Values denote means and ranges; figures in parentheses indicate number of animals studied.

Fig. 4 *Relationship between percentage disappearance of taurocholate from rat ileum and time.*

P. 25130

respectively. For all subsequent experiments a 20-min absorptive period was used unless otherwise stated. In other preliminary experiments the whole loop of ileum was removed, opened, washed with isotonic saline, saponified and counted for radioactivity as described by Dawson and Webb (1973). A constant but small percentage (<5%) of label was present in the tissue, confirming that luminal disappearance reflected absorption of TCA from the loop.

The effect of adding triolein (10 and 30 mmol/l), bovine serum albumin (3%) and ricinoleic acid (5 mmol/l) on TCA absorption is shown in the Table. None of these agents had a statistically significant effect on TCA absorption during the 20-min absorptive period. The effect of triolein (10 mmol/l) was studied at different absorptive periods from 1 to 40 min and had no effect on TCA absorption at any of these times.

Discussion

This study has shown pronounced quantitative and qualitative abnormalities in the distribution of duodenal bile salts in children with CF and pancreatic insufficiency after a test meal compared with control subjects.

The mean ratio of glycine:taurine conjugates (3·0) and the percentage of dihydroxy species (61%) in our control subjects are almost identical with those reported for normal adult bile (Heaton, 1972). The mean age of our control group was 40 months, an age when duodenal bile salts have previously been shown to be similar to those found in adults (Poley *et al.*, 1964). We have previously shown, using the same intubation procedure, that the concentration of total bile salts in duodenal juice varies during a 2-hour postprandial collection (McCollum *et al.*, 1977). In this study determinations were performed on an aliquot of the mixed postprandial collection, thus representing a mean of the postprandial concentration fluctuations. By definition this mean value will overestimate the lowest bile salt concentration during the postprandial period.

Table *Effect of triolein (TO), bovine serum albumin (BSA), and ricinoleic acid (RA) on the ileal absorption of taurocholate (TCA)*

	No. of animals	*Absorption of TCA (µmol/g wet weight ileum per 20 min)*
Controls	7	10·41±1·20
10 mmol TO/l	8	12·85±0·92
30 mmol TO/l	4	10·29±0·96
5 mmol RA/l	3	14·4±0·78
3% BSA	9	17·6±0·83

Absorptive values expressed as mean±1 SE.

Under the conditions of the present study 6 of the 11 CF patients with pancreatic insufficiency had total bile salt concentrations below our normal range, and in 3 the concentrations were below the critical micellar concentration (CMC), if this value is taken as 2 mmol/l. There was a marked increase in the ratio of glycine:taurine conjugates (mean 8·6), and a concomitant reduction in the percentage of dihydroxy bile salts (mean 37%); although these two qualitative abnormalities may be present in non-CF subjects during early infancy (Heaton, 1972), this cannot be the case in our older patients. The CMC is higher for trihydroxy compared with dihydroxy bile salts (Heaton, 1972), and the pKa of glycine conjugates (approximately 4·0) higher than that for taurine conjugates (approximately 2·0). These observations, coupled with the relatively low pH of the duodenal juice in some CF patients, would be anticipated to result in defective micellar solubilisation of lipid in CF, and contribute to the malabsorption of fat. This would be in keeping with the well established fact that pancreatic supplements only partially reduce the faecal losses of fat in most CF patients. Goodchild *et al.* (1975) using a different test meal after hormonal stimulation found mean total bile salt concentrations in duodenal juice to be no different in 5 CF patients compared with 2 adult controls. After stimulation with CCK-PZ and then secretin in the same patients the same authors reported mean bile salt concentrations (mmol/l/per 10 min) as 22·3 and 36·2 respectively. After stimulation with CCK-PZ the mean ratios of total trihydroxy:dihydroxy, and glycine to taurine conjugated bile salts were 1·9 and 5·2 respectively; these ratios show a similar trend to those which we observed although the glycine to taurine ratio in our patients was more pronounced. The marked discrepancies in total bile salt concentrations between the study of Goodchild *et al.* (1975) and ours may be related to technical differences. For example, intravenously administered CCK-PZ provides information on the maximal capacity of the pancreas to secrete its proteolytic juice and on maximal gallbladder contraction; in addition Goodchild *et al.* (1975) reported a reduced volume of duodenal fluid in response to hormonal stimulation, which might be anticipated to result in 'apparently' normal total bile salt concentrations. In the study of Goodchild *et al.* (1975) the test meal was administered soon after IV CCK-PZ and secretin, and bile salt data were reported for periods after both the hormonal stimuli and the test meal. The data after their test meal may not therefore accurately reflect the physiological events which are associated with entry of gastric contents into the proximal small intestinal lumen in CF, but rather the net response to maximal hormonal stimulation in addition to the test meal.

Marked increases in faecal output of bile salts have been reported in young children with CF (Weber *et al.*, 1973, 1976; Goodchild *et al.*, 1975), with reduced output (often within the normal range) in older children and young adults (Goodchild *et al.*, 1975; Roller and Kern, 1977). These observations together with our data are entirely consistent with a broken EHC secondary to defective absorption of bile salts by the distal ileum in young children with CF.

The pathophysiological mechanisms responsible for the broken EHC in CF have not been defined and raise intriguing and fundamental questions concerning bile salt metabolism in general. The ileal absorption of bile salts occurs by an active, carrier-mediated, sodium-dependent transport system which represents a highly efficient biological process for the conservation of the total bile salt pool of the body, and is basic to the maintenance of a normally operating EHC (Dowling, 1972). It has been suggested that the broken EHC in CF results from unhydrolysed triglycerides or other unhydrolysed dietary constituents interfering with the ileal absorption of bile salts (Weber *et al.*, 1973, 1976; Goodchild *et al.*, 1975; Watkins *et al.*, 1977). The finding of increased faecal bile salt outputs in other causes of pancreatic insufficiency lends support to this hypothesis (Goodchild *et al.*, 1975), as does the observation of Weber *et al.* (1973) who reported a good correlation between faecal bile salts and fat. This however, was not confirmed by Goodchild *et al.* (1975). In this context it is of interest that in the 2 patients with normal pancreatic enzymes in our study, duodenal bile salts were quantitatively and qualitatively normal. The relatively high concentrations of total bile salts in these 2 patients may be related to the reduced volume output of pancreatic secretions which occurs in CF, even in the absence of pancreatic insufficiency. The above observations prompted our studies on the possible effects of unhydrolysed fat and protein, as well as an hydroxy fatty acid, on the absorption of a bile salt in the terminal ileum of the rat *in vivo*.

High intraluminal concentrations of triolein, bovine serum albumin, and ricinoleic acid did not influence absorption rates of TCA in the rat ileum (see Table). Although caution should be exerted in extrapolating data from the experimental animal to man, our results do not appear to support the hypothesis that impaired pancreatic hydrolysis of dietary fat and protein (or the production of hydroxy fatty acids) plays a pathophysiological role in the broken EHC in CF.

There are a number of other explanations which can be considered. For example, there may be a defect in the mucosal phase of bile salt absorption which is unrelated to the nature of the luminal contents. This possibility rests on reports which have described increased faecal outputs of amino-acids (Gibbons *et al.*, 1969), impaired *in vitro* uptake of phenylalanine by small intestinal mucosa (Morin *et al.*, 1976), impaired vitamin B12 absorption (Deren *et al.*, 1973), and reduced mucosal lactase activity (Antonowicz *et al.*, 1968) in CF patients. It has also recently been shown using a steady state perfusion technique that the jejunal absorption of phenylalinine, but not lysine, is impaired in CF patients (P. Milla, personal communication). These two amino-acids are probably absorbed by separate transport systems (Matthews and Laster, 1965) which suggests that phenylalanine malabsorption may reflect a selective and primary defect of mucosal function in CF. These anormalities are not likely to be related to gross mucosal damage as the only described alterations of mucosal morphology in CF are dilated mucosal glands (Thomaidis and Arey, 1963) and thickening of surface mucus (Freye *et al.*, 1964). The possibility of a primary mucosal defect is supported by the finding that faecal bile salt losses in children with active coeliac disease are not significantly different from controls (Weber *et al.*, 1973), as the mucosal lesion in coeliac disease is predominantly a proximal one. This is not supported by a recent report in which marked reductions in faecal losses of bile salts were shown in older children and young adults with CF (Roller and Kern, 1977). The reason for the difference in bile salt excretion in older children and young adults compared with younger patients is not at present clear. A progressive reduction in the bile salt pool secondary to inadequate compensatory synthesis of bile salts by the liver is one possibility which requires further study; such a possibility is supported by the increased incidence of gallstones which occurs in older children with CF (Roy *et al.*, 1977). Alternatively more proximal regions of the small intestine may develop an increased capacity to absorb bile salts.

There is evidence that a component of pancreatic juice facilitates the absorption of vitamin B12 in the distal ileum (Toskes *et al.*, 1973), and a similar process could participate in bile salt absorption resulting in excessive faecal losses of bile salts in CF. It is difficult, however, to reconcile this possibility with the observed reduction in faecal bile salt losses which is associated with low fat or medium chain triglyceride diets in CF patients (Weber *et al.*, 1976).

The marked increases in faecal bile salt excretion in CF patients may have major clinical implications to the patient, and the pathophysiological mechanisms responsible for the broken EHC require further elucidation. Our animal studies, however, do not support the hypothesis that defective pancreatic hydrolysis of dietary substrates is responsible for the increased excretion of bile salts in this condition.

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Complete deficiency of adenine phosphoribosyltransferase

A third case presenting as renal stones in a young child

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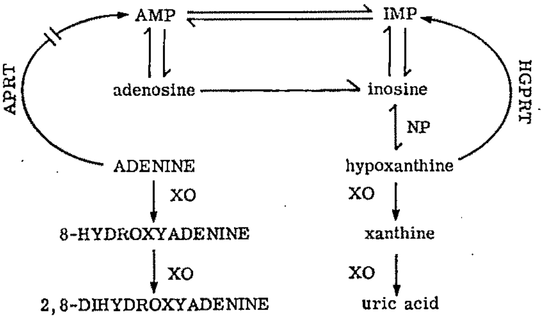
SUMMARY We report a third case of 2, 8-dihydroxyadenine stones in a child with a complete lack of the adenine salvage enzyme—adenine phosphoribosyltransferase (APRT). The propositus, a 20-month-old girl of consanguineous Arab parents, presented with multiple urinary tract infections and supposed 'uric acid' stones in the right renal pelvis and left ureter. Both parents and one brother were heterozygotes for the defect, in keeping with an autosomal recessive mode of inheritance. In contrast with the other purine salvage enzyme disorder of childhood with true uric acid stones (the Lesch-Nyhan syndrome), uric acid excretion was normal in all family members. As in our previous case, treatment with allopurinol, without alkali, has eliminated the urinary excretion of 2, 8-dihydroxyadenine: the stones were removed surgically. 2, 8-Dihydroxyadenine should be considered in any child thought to have uric acid stones and tests made to distinguish the two compounds.

Many urinary stones or crystals identified in children result from the overexcretion of normally minor urinary constituents, compounds of limited solubility whose overexcretion may be the direct consequence of a block in an essential step in a metabolic pathway. Examples are found in hereditary oroticaciduria (Smith *et al.*, 1972), xanthinuria (Dent and Philpot, 1954), and the Lesch-Nyhan syndrome (Nyhan, 1973). In the Lesch-Nyhan syndrome, uric acid stones or gravel form because of gross overproduction of uric acid arising from a lack of the hypoxanthine salvage enzyme–hypoxanthine-guanine phosphoribosyltransferase (HGPRT: EC 2.4.2.8) (Fig. 1). These children also have bizarre neurological complications and other clinical manifestations (Nyhan, 1973).



APRT = adenine phosphroibosyltransferase; HGPRT = hypoxanthine guanine phosphoribosyltransferase; NP = nucleoside phosphorylase; XO = xanthine oxidase; AMP = adenosine monophosphate (adenylate); IMP = inosine monophosphate (inosinate).

Fig. 1 *Metabolic pathways of purine degradation and salvage illustrating the origin of 2, 8-dihydroxyadenine. In the absence of APRT, adenine becomes available for oxidation by xanthine oxidase to hydroxy- then dihydroxyadenine, in a fashion analogous to the production of uric acid from hypoxanthine. In man, adenine cannot be converted to adenosine by nucleoside phosphorylase as hypoxanthine may be converted to inosine, so this route is not available for disposal of adenine. The only alternative pathway is oxidation.*

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A complete lack of the other purine salvage enzyme—adenine phosphoribosyltransferase (APRT: EC 2.4.2.7)—was described in children of two separate families, one in France (Cartier and Hamet, 1974; Debray *et al.*, 1976) and the other from our own unit (Simmonds *et al.*, 1976a, b; Van Acker *et al.*, 1977). Children with this deficiency also present with urolithiasis, because of the excretion of 2, 8-dihydroxyadenine, an extremely insoluble analogue of uric acid (Fig. 1). The excretion of this compound follows the accumulation of adenine in the absence of the salvage enzyme, APRT, and its oxidation by xanthine oxidase via the 8-hydroxy intermediate (Fig. 1) (Bendich *et al.*, 1950).

We report studies in a third family with a complete lack of the APRT enzyme. Stones of 2, 8-dihydroxyadenine were present in the daughter. As in the two previous cases, the stones were first mistaken for uric acid because 2, 8-dihydroxyadenine and uric acid are indistinguishable in chemical tests used routinely for identifying uric acid stones (Simmonds *et al.*, 1978).

Clinical data

The patient was born in August 1975, the 3rd child of consanguineous Arab parents (Fig. 2). Birth was normal and she was well until aged one year, when she began to suffer repeated attacks of abdominal pain and fever. These were diagnosed as urinary tract infections and, in May 1977, she was referred, aged 21 months, for investigation of lithiasis. An IVU showed a nonfunctioning left kidney, and a radiolucent calculus in the pelvis of the right kidney (Fig. 3). She was 81 cm in height, 10·0 kg in weight, and had red hair. Neither kidney was tender or palpable, and neurological examination was normal. However, urine culture showed a growth of $>10^5$ *Klebsiella aerogenes*/ml, with numerous leucocytes, red cells, and debris. Hb was 11·6 g/dl, WBC 14 400 /mm^3 (14·4 × 10^9/l). Plasma electrolytes were normal, with blood urea 4·5 and 3·4 mmol/l (27 and 20 mg/100 ml). Plasma creatinine was initially 40 μmol/l (0·45 mg/100 ml), but later was 100 and 120 μmol/l (1·13 and 1·36 mg/100 ml). Serum urate was 0·24 mmol/l (4 mg/100 ml) by a nonspecific colorimetric method. The differential diagnosis of uric acid, or 2, 8-dihydroxyadenine urolithiasis was considered.

At the 1st operation (May 1977) cystoscopy and ureteric catheterisation showed a block in the left ureter 2 cm from the bladder. This calculus was removed by ureterolithotomy, and the stone in the pelvis of the right kidney was removed later at the same operation. Both stones were friable and greyish in colour. The urinary infection was treated with cephalexin 125 mg four times a day.

Examination of the stones by thermogravimetric analysis (Rose and Woodfine, 1976) suggested uric acid, but further examination by wet chemistry (Westbury and Omenoger, 1970) and by other specific techniques (see Methods) showed them to be composed of almost pure 2, 8-dihydroxyadenine (Simmonds *et al.*, 1978). Studies of urinary purines

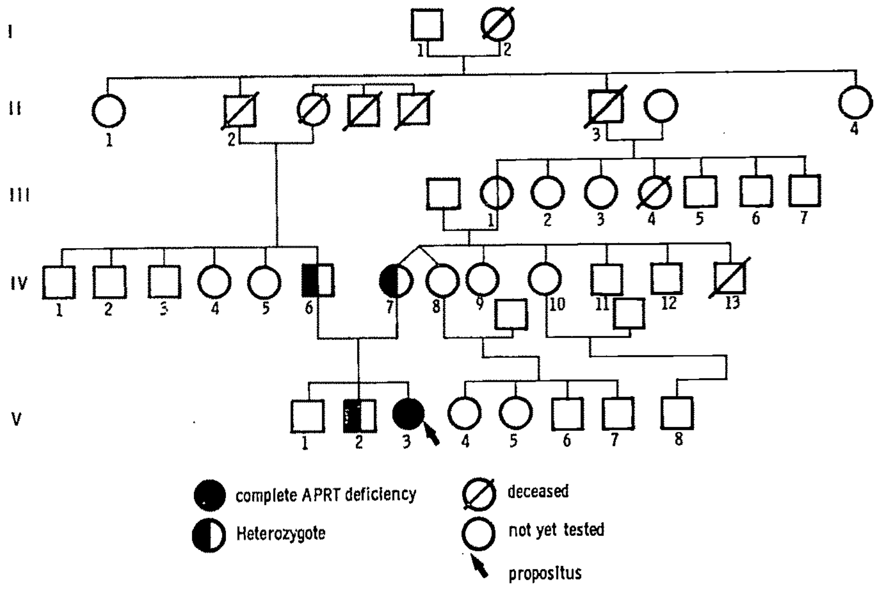

Fig. 2 *The family of the propositus. None of the other members of the family has dihydroxyadenine stones, but only the immediate family was tested for APRT activity (Table 2). Consanguinity is present, the father's grandparents and and the mother's great-grandparents being the same.*

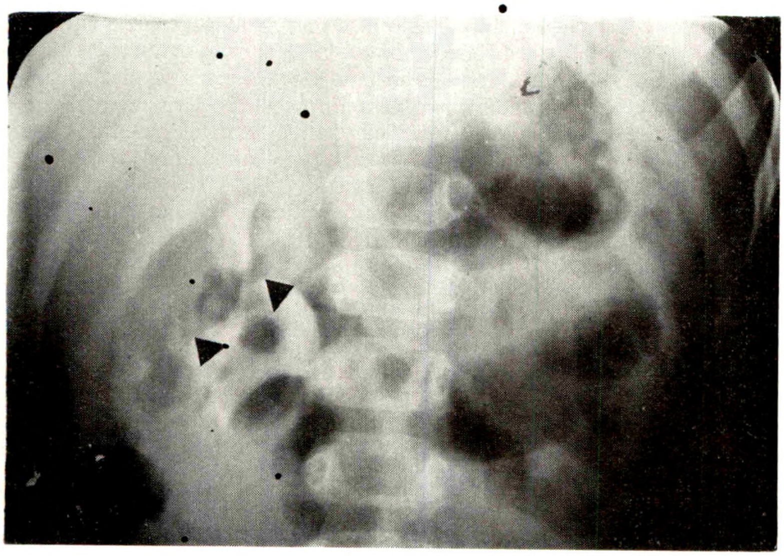

Fig. 3 *IVU taken in May 1977 when patient was aged 21 months. The left kidney does not function at all, and there is a large radiolucent stone (arrow) in the pelvis of the right kidney.*

and purine enzyme activities showed complete lack of APRT (see Methods and Results).

The child was treated with allopurinol 10 mg/kg per 24 h and she returned home. Three months later, in August 1977, she returned for more extensive examination. In the interval she had had several more urinary tract infections, treated with cephalexin and nitrofurantoin. In two of these, *Kl. aerogenes* was again grown from the urine, and in the 3rd attack—*Escherichia coli*. Otherwise she was well and had grown 1·6 kg, and 4 cm in height. Examination of renal function showed a glomerular filtration rate of 90 ml/min per 1·73 m², with only 13% of renal function from the left kidney, as judged by scanning with DMSA. Plasma creatinine was 50, 46, and 56 μmol/l (0·56, 0·52, and 0·63 mg/100ml) and blood urea 3·0, 4·1, and 6·0 mmol/l (18, 24, 36 mg/100 ml). Urine culture showed *Klebsiella*. IVU and micturating cystography showed a doubtful calculus in the right renal pelvis, and several stones in a grossly refluxing left ureter and pelvis (Fig. 4).

At the 2nd operation the left renal parenchyma appeared reasonably well preserved, and the stones were removed from the left by ureter pyelolithotomy and ureterolithotomy. A stricture at the site of the previous removal of stone from the left ureter was repaired. At a 3rd operation (September 1977), retrograde catheterisation of the right urinary tract showed 2 stones in the pelvis of the right kidney similar to those removed previously: these were extracted.

The *Klebsiella* infection was again treated with cephalexin, followed by co-trimoxazole, and the allopurinol dosage increased to 20 mg/kg per 24 h; on this dose the urine became free of 2, 8-dihydroxyadenine. Because of the risk of xanthine or oxipurinol calculi, this dosage was later reduced to 15 mg/kg per 24 h, and the child returned home on this treatment.

During the period of investigation of the propositus, her father suffered from an episode of renal colic, but the stone passed was subsequently identified as pure calcium oxalate.

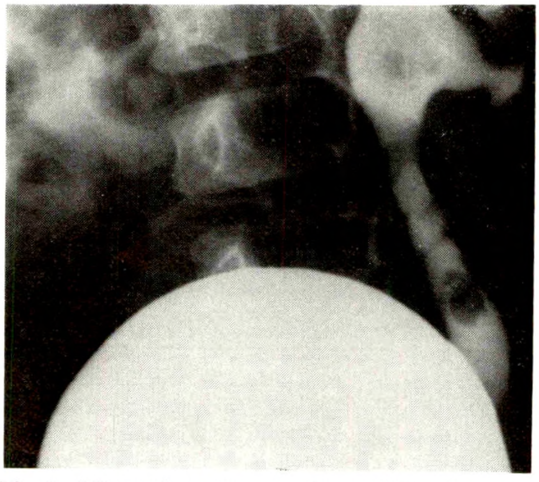

Fig. 4 *Micturating cystogram, August 1977, when patient was aged 24 months. There is reflux of contrast medium into the left urinary tract, and several stones are present in the pelvis and ureter. There is also a ureteric stricture at the site of previous stone removal.*

Methods

Stone analysis was carried out by methods already reported (Simmonds *et al.*, 1976 a, b; Rose and Woodfine, 1976). Methods used in the identification and quantitation of urinary purine metabolites by chromatography and 2-dimensional high-voltage electrophoresis have also been reported previously (Simmonds, 1969). A new rapid and simple method, isotachophoresis of the urine, has also been investigated (Simmonds *et al.*, 1978; Sahota *et al.*, in preparation) and appears to have potential for screening for homozygotes for APRT deficiency.

APRT activity was estimated in both intact (Dean *et al.*, 1978) and lysed erythrocytes, as previously described (Cartier and Hamet, 1968; Van Acker *et al.*, 1977). Blood from the child, her parents, and from her two brothers (aged 12 and 9 years) was taken in the fasting state and centrifuged and separated immediately. 24-hour urine collections were made on a low-purine, caffeine-free diet with toluene as preservative. A 15-hour water deprivation test was performed.

Routine biochemistry was investigated using a Vickers multichannel automated analyser. Complement components C3 and C4 were assayed by radial immunodiffusion using monospecific antisera; haemolytic complement by a plate assay incorporating EA, and serum lipid levels were also measured by standard automated procedures. Lymphocytes were obtained from our patient and her parents; transformation in response to stimulation with PHA, pokeweed and concanavalin A were studied using ^{3}H-thymidine incorporation as indicator of response (Panayi and Corrigall, 1977).

Results

Urinary purine metabolites. Detailed results of the stone identification have been reported (Simmonds *et al.*, 1978).

Urinary purine levels on four separate occasions in our patient are given in Table 1. Total adenine metabolites in each varied between 34 and 28% of the total purine metabolites, the latter being normal when expressed as mmol/kg per 24 h. Plasma uric acid levels were normal in our patient (Table 2) and in her parents on a low purine diet. Urinary uric acid levels were normal in the child, but at the upper limit of normal for her parents. Plasma uric acid levels were also normal in the two brothers (Table 2). Ultraviolet scans obtained using separation of

Table 1 *Purine and pyrazolophyrimidine excretion (mmol/24 h) in a homozygote for APRT deficiency*

	*12 May (mmol/l)**	*Hypothetical mmol/24h based on pseudouridine excretion*	*16 August*	*21 September*	*19 October*
Pseudouridine	0·758	0·15	0·12	0·13	0·13
Uric acid	1·023	0·205	0·21	0·37	0·37
Xanthine	0·046	0·009	0·09	0·09	0·17
Hypoxanthine	0·051	0·010	0·16	0·02	0·05
Adenine	0·19	0·035	0·11	0·12	0·20
8-OH adenine	0·09	0·018	Not detected	0·04	0·03
2, 8-diOH adenine	0·32	0·064	0·04	0·04	Negligible
Total		0·34	0·51	0·66	0·82
Dosage			0·73 (10 mg/kg)	0·73 (10 mg/kg)	1·47 (20 mg/kg)
Allopurinol			0·04	0·06	0·27
Oxipurinol			0·34	0·39	0·64
Oxipurinol riboside			0·06	Not detected	Not detected
Allopurinol riboside			0·09	0·04	0·18
Total			0·53	0·49	1·09
Dose excreted (%)			72	67	74

*Random sample—24-hour urine collection not possible.

Table 2 *Purine salvage enzyme activity† (APRT and HGPRT) and uric acid levels in a family with APRT deficiency*

Date (1977)		*Patient*	*Father*	*Mother*	*Brother (12 years)*	*Brother (9 years)*
16 August	APRT§	0·61	5·06	7·33	23·38	7·57
16 August	HGPRT§	122·22	124·25	126·15	109·58	96·43
12 May	Plasma uric acid	3·3 (0·20)†	5·0 (0·30)†	3·0 (0·18)†	Not tested	Not tested
16 August	mg/100 ml(mmol/l)	1·8 (0·11)‡	7·0 (0·42)	3·7 (0·22)	3·7 (0·22)	3·4 (0·20)
12 May	Urinary uric acid	36 (0·21)*	631 (3·75)	415 (2·47)	Not tested	Not tested
16 August	mg/24h (mmol/24h)	36 (0·21)‡				

*Estimated (see Table 1); †low purine, caffeine-free diet (all other results are on a normal diet); ‡on allopurinol.

§Nmol of base converted per mg Hb/h

Control		APRT	HGPRT
	child	28·15	118·5
	adult	21·35	136·7

urinary purines by isotachophoresis (not shown) showed the presence of the abnormal and diagnostic metabolite adenine only in the case of the homozygote; the scan in her case, as in the previous homozygotes, being otherwise indistinguishable from that of a healthy control (Simmonds *et al.*, 1978).

Effect of allopurinol therapy. Total allopurinol metabolites are also given in Table 1; the percentage of the administered dose absorbed and excreted being relatively constant (67–74%) and similar to that in the previous case studied by us (Simmonds *et al.*, 1977; Van Acker *et al.*, 1977) and in healthy controls (Simmonds, 1969). At a dose of 10 mg/kg per 24 h the principal metabolite of allopurinol was oxipurinol. At the higher dose (20 mg/kg per 24 h) increased amounts of unchanged allopurinol and its riboside were detected in the urine, indicating effective inhibition of xanthine oxidase at this dosage. In agreement with this was the absence of detectable 2,8-dihydroxyadenine excretion at the higher dosage. This was accompanied by an increment in the urinary adenine levels, as anticipated, but without any reduction in total purine excretion, in contrast with the situation in a control child, both as noted in our previous case (Van Acker *et al.*, 1977).

Other investigations. Other biochemical investigations, including fasting serum cholesterol and triglyceride concentrations, were essentially normal. The results of the lymphocyte transformation studies were within the lower limit of the normal range for adults in the case of the heterozygotes, and apparently normal for a child of the age of our patient as were complement levels (C3, C4, and total haemolytic complement) in all family members.

Water deprivation tests showed a normal ability to concentrate the urine above 900 mmol/kg in the father and the two brothers. The mother's result was slightly lower, while the patient showed a complete inability to concentrate the urine, compatible with her urinary tract infection and stones. Renal function, as measured by creatinine clearance, was not reduced in other members of this family.

Discussion

This patient is the third in whom 2, 8-dihydroxyadenine stones have been identified as a result of a complete lack of the salvage enzyme—APRT. In all three patients the stones were initially confused with uric acid stones. A brother of the second patient was asymptomatic, although he, too, lacked the enzyme, suggesting that the defect was relatively benign in that it can occur without clinical manifestations. Studies in this third patient have confirmed this and show that children with this defect are clinically normal, apart from having urolithiasis. Correction of their renal complication will allow them to lead a normal life, unlike children with the Lesch-Nyhan syndrome.

Partial APRT deficiency has been described in five separate families, but these cases were discovered during screening for HGPRT deficiency. The association between partial APRT deficiency, gout, and hyperuricaemia, described in some of these families, now appears fortuitous (Kelley *et al.*, 1968; Delbarre *et al.*, 1974; Emmerson *et al.*, 1974, 1975; Fox and Kelley, 1974). Two recent reports (Emmerson *et al.*, 1977; Fox, 1977), have put the incidence of heterozygosity for APRT deficiency at somewhere between 0·5 and 1%.

The discovery of another patient with complete lack of APRT so soon after our other one suggests that the condition may previously have been misdiagnosed, and is more common than its description suggests (Cartier and Hamet, 1974; Simmonds *et al.*, 1976a; Van Acker *et al.*, 1977). The urinary metabolites excreted by the child, as in the previous cases, are a direct consequence of the enzyme defect; in the absence of the APRT enzyme the only alternative metabolic route for adenine is oxidation by xanthine oxidase via the 8-hydroxy intermediate to the extremely insoluble 2, 8-dihydroxyadenine (Fig. 1). Because of its similar structure (Fig. 1) it reacts mole for mole as uric acid during routine chemical testing; hence its frequent misdiagnosis.

An interesting observation, previously noted in both the other affected children and now confirmed, is that total purine end-product including uric acid appears essentially normal. This is surprising in view of the fact that adenine nucleotides with guanine nucleotides have been considered to exert feedback inhibitory control of *de novo* purine production; and absence of the analogous enzyme, HGPRT, in the Lesch-Nyhan syndrome is associated with gross overproduction of uric acid. The normal results in APRT deficiency would suggest that endogenous adenine production is neither extensive nor critical for the overall control of purine production in man. This is in keeping with a dietary origin suggested for the adenine in this defect (Simmonds *et al.*, 1977; Van Acker *et al.*, 1977).

Correction of the urolithiasis in this defect will allow the children to lead a normal life, unlike children with the Lesch-Nyhan syndrome in whom treatment did not lead to an improvement in the mental or neurological parameters. Interestingly, the father of our patient, as did the father of our previous patient, suffered an episode of renal colic with the passage of oxalate stones. The urinary uric acid level in both men is in the upper limit of normal. Xanthine

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oxidase inhibition will obviously prevent 2, 8-dihydroxyadenine formation (Fig. 1) and allopurinol, a xanthine oxidase inhibitor, will therefore be the drug of choice. The common practice of alkalinisation of the urine for uric acid stones (De Vries and Sperling, 1975) will be ineffective in 2, 8-dihydroxyadeninuria, as the solubility of this compound does not alter within the physiological pH range (Debray *et al.*, 1976). It may even be harmful, since allopurinol plus alkali was ineffective in controlling stone formation in our previous patient (Van Acker *et al.*, 1977), whereas allopurinol alone at a dose of 10 mg/kg per 24 h resulted in immediate cessation of stone formation and crystalluria. A higher dose, 20 mg/kg per 24 h, was necessary to produce the same effect in our present patient, but this may have been due to the presence of stones not removed at the initial operation, in the meantime she is being treated with an intermediate dose, 15 mg/kg per 24 h. As the excretion of adenine metabolites was much greater when our previous patient was on a high rather than a low purine diet we also suggest that a low purine diet be given together with appropriate allopurinol dosage. This may be important as free adenine is not normally present in man for any length of time. APRT-deficient children being treated with allopurinol are testing the *in vivo* toxicity of free adenine. They should therefore be watched carefully, and undergo frequent checks for alteration in any other clinical or biochemical parameters.

Enzyme studies in erythrocyte lysates have confirmed heterozygosity in the parents and the complete deficiency in the child. One brother is also heterozygous, which would be in keeping with the autosomal mode of inheritance suggested in previous studies (Emmerson *et al.*, 1977; Van Acker *et al.*, 1977).

Studies in intact erythrocytes have shown that at normal physiological concentrations of adenine, heterozygotes are indistinguishable from normal individuals; while at higher substrate concentration results comparable with those in erthrocyte lysates are obtained (Dean *et al.*, 1978). This would explain why heterozygotes are essentially normal, since they can cope with normal loads of dietary adenine.

The reason why 2, 8-dihydroxyadenine stones were confused with uric acid stones is the subject of a separate report (Simmonds *et al.*, 1978). Even if specialised techniques are not available, the following clues may help to distinguish children with the defect: uric acid stones are hard and yellow, while 2, 8-dihydroxyadenine stones are friable and greyish-blue on crushing. Uric acid levels in plasma and urine will also be normal in 2, 8-dihydroxyadeninuria. The children are otherwise clinically normal, and have no neurological symptoms or signs. We suggest that any child who is thought to have uric acid stones should have stones and urine examined more closely. If possible, the stones should be submitted for specialised confirmatory studies.

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The lungs in congenital bilateral renal agenesis and dysplasia

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SUMMARY A detailed quantitative analysis was made of the lungs from 8 infants dying with bilateral renal agenesis or dysplasia. Total lung volume was reduced in all cases, particularly in those with renal agenesis. In both groups there was a reduction in number of airway generations, indicating interference with development at between 12 and 16 weeks' gestation. The alveoli in each acinus were reduced in size and, in some cases, number—although their stage of differentiation was normal for age—pointing to a disturbance of growth during later fetal life also. As liquor is largely non-renal in origin at least up to 16 weeks' gestation, it seems that there are factors other than the oligohydramnios interfering in early lung growth in these cases, such as reduced proline production by the kidney.

The concurrence of bilateral renal agenesis and pulmonary hypoplasia was first recognised by Potter (1946) and later confirmed by others (Davidson and Ross, 1954; Sylvester and Hughes, 1954; Carpentier and Potter, 1959; Potter, 1965). Later it became apparent that lethal pulmonary hypoplasia was also a consistent feature in babies with no renal function at birth because of bilateral renal dysplasia with or without cyst formation (Ashley and Mostofi, 1960; Bain and Scott, 1960). The underlying mechanism remains obscure although many have suggested that the pulmonary hypoplasia is secondary to oligohydramnios and thoracic compression *in utero*. Siblings are only rarely affected (Buchta *et al.*, 1973; Whitehouse and Mountrose, 1973; Cain *et al.*, 1974; Hack *et al.*, 1974) and there are few reports of both members of a twin pair being affected (Mauer *et al.*, 1974). Oligohydramnios is almost universal, breech presentations and premature labour are frequent, stillbirth is not uncommon (Ratten *et al.*, 1973), and early neonatal death due to respiratory insufficiency is almost inevitable in those born alive. Babies surviving for any time often develop a complicating pneumothorax or pneumomediastinum (Liberman *et al.*, 1969; Renert *et al.*, 1972; Stern *et al.*, 1972; Bashour and Balfe, 1977) and a chest *x*-ray taken at this time may be almost diagnostic (Leonidas *et al.*, 1975). In a series of 49 cases of bilateral renal agenesis, Potter (1961) found at necropsy that the degree of pulmonary hypoplasia varied, but in extreme cases alveoli were almost completely lacking. Reale and Esterly (1973) found a reduced lung to body weight ratio in 20 infants with a variety of renal anomalies. This was greatest in those cases with bilateral agenesis. They also found in some, a reduction in the number of alveoli within each acinus, assessed by the method of Emery and Mithal (1960).

The nature of the hypoplasia in the lungs from infants with congenital diaphragmatic hernia (Kitagawa *et al.*, 1971) and rhesus isoimmunisation (Chamberlain *et al.*, 1977) was analysed by precise morphometric techniques after injection of the pulmonary artery and inflation of the lung. In both conditions the number of airway generations and their accompanying arteries are reduced as well as the total number of alveoli. In the present study, these quantitative methods have been applied to lungs from infants with bilateral renal agenesis or dysplasia. Using these methods, it is possible to analyse type and degree of hypoplasia and the timing of interference with development.

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Case material

The lungs from 8 patients with abnormal kidneys were studied and the diagnosis and main features are shown in Table 1. Cases 1 and 2 had bilateral renal agenesis. Case 1 also had sacral agenesis, gross rotation of both lower limbs, and rectal atresia. Three infants (Cases 3–5) were diagnosed as having the typical features of sirenomelia (Duhamel, 1961) which included in these cases bilateral renal agenesis. Cases 1–5 are all referred to as having renal agenesis. Cases 6–8 had renal dysplasia, the kidneys consisting of a mass of watery cysts with no renal tissue (Pathak and Williams, 1964). Case 7 also had hydrocephalus and was thought to have the Dandy-Walker syndrome (D'Agostino *et al.*, 1963). Case 6 was one of twins, the other being anencephalic. In all patients it was reported that little or no liquor was present at birth and amnion nodosum (Landing, 1950) was proved in Cases 1, 2, 5, 7, and 8. All 8 showed evidence of postural moulding. Two babies were stillborn, 5 died of respiratory insufficiency, and one (Case 7) from intracranial haemorrhage. The longest period of survival was 18 hours.

The 2 infants with renal agenesis born before the 31st week of gestation were of normal weight for age but the weight of the others with agenesis was reduced to the 5th centile or less. The infants with renal dysplasia were of normal body weight, except for Case 6 which was on the 10th centile, probably because it was one of twins. In the 4 infants in which it was measured, combined heart and lung weight was reduced. Pressure-volume curves (Reynolds *et al.*, 1968), obtained on all but Case 4, showed that all lungs were reduced in volume, particularly those with renal agenesis. The relationship of volume to pressure change was normal in Cases 2, 3, 7, and 8 showing normal alveolar stability. In Cases 1, 5, and 6 although there was some residual air indicating that surfactant was present, there was a relatively rapid decline in volume with decreasing pressure.

Methods

The pulmonary arteries of the 8 cases were injected with a barium sulphate and gelatine suspension at 60°C and at a water pressure of 100 cm. Arteries were filled and fully distended down to precapillary level. The airways were inflated with buffered formol saline at a pressure of 45·5 cm water and the lungs and heart left to fix for at least one week. The lungs were studied, using quantitative techniques as described by Hislop and Reid (1970). These studies included measurement of inflated lung volume, measurement of lung length and pulmonary artery size on arteriograms, and tracing airway branching pattern by serial reconstruction. The maturity of the alveoli was assessed, size was estimated from the number per unit area, and to estimate alveolar number per acinus the radial alveolar count, as described by Emery and Mithal (1960), was used. Wall thickness of pulmonary arteries was measured and the degree of extension of muscle along the arterial pathways assessed by identifying arteries according to their accompanying airways and their size (Davies and Reid, 1970). After fixation, the hearts were dissected and weighed using the method of Fulton *et al.* (1952).

Results

The morphological findings are summarised in Table 2.

Table 1 *General necropsy findings*

Case no.	*Sex*	*Gestational age (weeks)*	*Survival time (min)*	*Body weight*		*Inflation volume (ml)*	*Alveolar stability*	*Diagnosis*	*Comment*
				(kg)	*(Centile)*				
1	M	29	15	1·2	50	3	?N	Bilateral renal agenesis	Rectal atresia and sacral agenesis
2	M	33	18 hours	1·25	5	9	N	Bilateral renal agenesis	Bilateral hip dislocation
3	F	30	10	1·44	50	7	N	Sirenomelia and bilateral renal agenesis	
4	M	38	Stillborn	1·71	<5	10	—	Sirenomelia and bilateral renal agenesis	
5	F	41	Stillborn	2·19	<5	5·5	?N	Sirenomelia and bilateral renal agenesis	
6	F	38	70	2·49	10	14	?N	*Bilateral multicystic renal dysplasia	Identical twin anencephalic
7	F	39	25	3·17	50	16	N	†Bilateral polycystic kidneys	Hydrocephalus with Dandy-Walker deformity. Sibling also affected
8	F	41	120	3·63	75	18	N	Bilateral multicystic renal dysplasia	Right hip dislocation

*Royer *et al.* (1974); †Goldston *et al.* (1963)

Table 2 *Morphological findings*

Case no.	*Gestational age (weeks)*	*Lung volume (ml)*	*Airway no.* (normal 20–25)*	*Alveolar*		*Radial alveolar count*	*Artery size*	*Arterial wall thickness*	*Arterial muscle extension*		*Total ventricular weight (g)*
				maturity	*size*				*By size*	*By position*	
1	29	12 (55)†	—	N	↓↓	2·5 (2·6)‡	↓	N	↑	↑	3·25 (3·7)§§
2	33	17 (70)	16	N	↓	2·3 (3·7)	N	↓	↑	↑	1·68 (5·2)
3	30	14 (60)	17	N	↓↓	2·1 (2·6)	N	↓	↑	↑	3·75 (4·0)
4	38	18 (80)	—	N	↓↓	2·7 (3·6)	↓	↓	↓	↓	5·66 (12·1)
5	41	19 (110)	—	N	↓↓	3·1 (4·4)	↓	(↓)	Normal	↓	3·87 (12·3)
6	38	30 (80)	—	N	↓↓	3·5 (3·6)	↓	Normal	Normal	Normal	7·58 (12·1)
7	39	22 (95)	20	N	↓↓	2·5 (3·6)	↓	↑↑	↑	↑	11·71 (12·2)
8	41	25 (110)	18	N	↓	3·0 (4·4)	↓	N	↑	↑	10·91 (12·3)

*Normal values. Hayward and Reid (1952); †Hislop (1971); ‡Emery and Mithal (1960); §§ Hislop and Reid (1972a).
↑—increase in size, number or extension to the periphery; ↓—decrease in size, number or extension to the periphery.

Lung volume. All lungs were greatly reduced in volume. In Cases 1–5 the reduction was greatest, the volume being similar to that of a fetus of about 24 weeks' gestation, and in none was it more than one-quarter of the expected volume. In Cases 6–8 the volume was equivalent to the normal lung at 28 weeks' gestation. In all cases lung length was appropriate for volume.

Airways. In Cases 2, 3, 7, and 8 the posterior basal airway to the left lower lobe was traced from hilum to terminal bronchiolus by dissection and microscopical serial reconstruction. While the normal number of airway generations for this segment is 20–25 (Hayward and Reid, 1952), in all 4 pathways the number was reduced to between 16 and 20 generations. It seemed that the bronchi (the airways which develop first and have cartilage in their wall) were normal in number while the bronchioli (which appear later and lie distal to the cartilage plates) were considerably reduced. Unlike the others, Case 7 had a more nearly normal number of bronchioli. In addition, in Cases 1–5, microscopical examinations showed bronchi abnormally close to the pleura, indicating relative reduction in volume of the respiratory region and of the number of peripheral airways. In Cases 1 and 2, the cartilage plates were large for the size of the airways. In Cases 6–8 distribution of airways was normal.

Alveoli. The development of the alveoli was assessed by their stage of maturation, their number, and size. Judged by gestational age, the lungs should have been in the terminal sac stage of development (Boyden, 1975). At the beginning of this stage, at 24 weeks' gestation, the saccules are simple in outline; by its end, at birth, primitive alveoli are seen in their walls as shallow indentations. In all lungs the alveoli were of normal type for age but were smaller than normal.

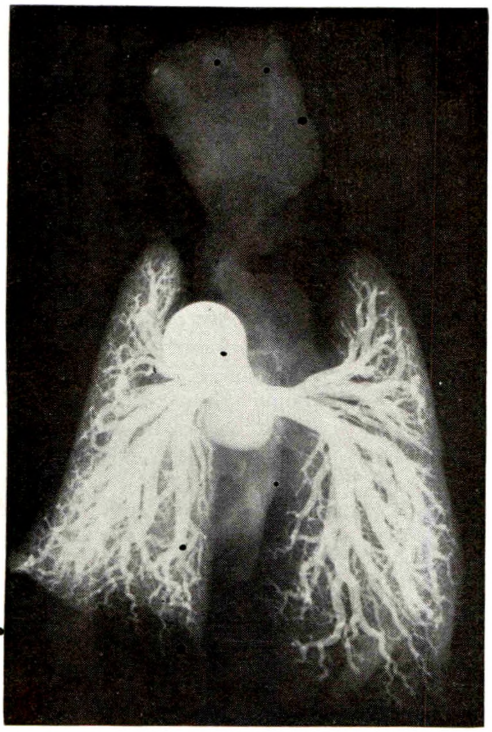
Radial alveolar counts showed that in Cases 2, 4, 5, 7, and 8 the number of alveoli in each acinus was more than 1 SD below the normal mean (Emery and Mithal, 1960). In the other 3 cases it was below the mean but within the normal range. As the reduced number of airway generations means a reduced acinar number, it may be assumed that in all lungs the total number of alveoli must be reduced. Thus reduction in alveolar number and size both contribute to the reduced total lung volume.

Pulmonary arteries. From the arteriograms, the overall branching pattern and size of the pulmonary arteries were assessed (Fig. 1).

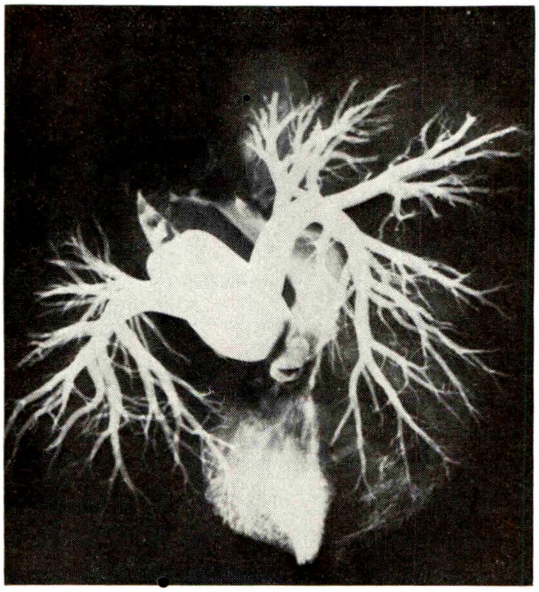
In Cases 2 and 3 the arteries were normal in size for age of the fetus. In the other 6 lungs the arteries were reduced in size for age, although in each the arteries were large for the volume of the lung. This relative increase was greater in the infants with renal agenesis and in these the arteries appeared large, tortuous, and crowded. This was confirmed microscopically, where large vessels were found close to the pleura. The arteriograms of the renal dysplasia lungs showed normal distribution of vessels and no relative increase in size of peripheral arteries.

Arteries accompany airways and the reduction in the total number of preacinar conventional arteries mirrored reduction in airway number. Supernumerary arteries were present but appropriately reduced in number. The number of arteries per unit area within the acinus was less than normal in the lungs associated with renal agenesis but seemed normal in those with renal dysplasia.

Muscularity of pulmonary arteries. In cases of agenesis (Cases 1–5) the wall thickness of the pulmonary arteries was less than the normal fetal level except in one, the youngest, in which it was at normal fetal level. In case 2 the walls were as thin as in a normal adult—1–2% in the larger vessels.



(*a*)



(*b*)

Figure. *Arteriogram of the lung of* (*a*) *Case 2* (*renal agenesis*) *and* (*b*) *Case 8* (*renal dysplasia*) (× *1*). *The arteries have been injected with a radio-opaque medium.*

In two cases of dysplasia (Cases 6 and 8) wall thickness was at normal fetal level and in the 3rd it was thicker than normal. This case also had an increase in pulmonary vein wall muscle while in all others vein walls were normal.

Muscularity was also assessed by estimating the size of vessels with muscular walls and also the level within the lung to which muscular arteries extended. The pattern of muscularity did not correlate with renal diagnosis nor did it correlate with alveolar development. In 4 patients with agenesis and 2 with dysplasia, the muscle extended into smaller and more peripheral vessels than normal. One patient with agenesis and one with dysplasia had normal muscle distribution by size but less muscle within the acinus, and one patient with agenesis had less arterial muscle, both by size and position, than normal.

Heart weight. The ventricles of the heart were dissected and weighed and the ratio between weight of left ventricle plus septum and right ventricle estimated. In all patients the ratio was in the normal fetal range, between 1 and 2 (Hislop and Reid, 1972a). Total heart weight was less than expected for gestational age in 3 of the 5 patients with renal agenesis and in 2 of these it was reduced even for the reduced body weight. Of the 3 infants with renal dysplasia, heart weight was normal in 2 and reduced in the 3rd but this infant was small, being a twin, and the heart to body weight ratio was normal.

Discussion

These cases with renal agenesis or dysplasia are further illustrations of Potter's observation that the lungs from infants with bilateral renal agenesis are hypoplastic (Potter, 1946). Precise morphometric techniques have now made it possible to analyse separately the several structural constituents of the lung and to detect the presence and define the degree of hypoplasia in each. The abnormality can be interpreted according to the schedule of normal fetal development previously described (Bucher and Reid, 1961; Hislop and Reid, 1972b). Although many of the changes in the lungs were similar in patients with either agenesis or dysplasia, there were features sufficiently different to suggest that in these two conditions the severity or timing of interference may have been different or even that a different factor may have operated.

Pathological changes. Total lung volume was reduced in all cases but particularly so in patients with renal agenesis. Reale and Esterly (1973) found that cases with bilateral renal agenesis had the lowest lung weight/body weight ratio when compared with other types of kidney anomalies. In the present series however, lung volume/body weight ratio was similar in both groups.

Airways and alveoli. The reduction in number of airway generations suggested an arrest in development at between 12 and 16 weeks' gestation because only the broncholi were affected (Bucher and Reid, 1961). It may be that the precise time of effect or the degree of sensitivity at this time explains the greater reduction in renal agenesis. In both groups the drop in airway number must lead to a reduction in number of acini. In the babies with renal agenesis, growth within the acinar region as well as of airways was thought to be reduced because microscopically the respiratory region was small even for the reduced airway number, and the cartilage plates and airways were disproprortionately large when related to lung volume. A relatively greater reduction in the respiratory region has also been reported in one case of thoracic dystrophy by Finegold *et al.* (1971) and in congenital diaphragmatic hernia by Kitagawa *et al.* (1971). The disproportion was not seen in the dysplastic patients. In all lungs the reduced respiratory region was due partly to fewer acini because of fewer airway generations and partly to the small size of alveoli; in 5 cases, in addition, the number of alveoli per acinus was clearly reduced.

In infants with renal agenesis, Potter (1965) described in uninflated lungs, immaturity of the alveolar region, some lungs apparently having no alveoli at all. In the present series there was normal maturity of alveoli.

Arteries. In both renal agenesis and dysplasia, arterial number was reduced and probably followed the reduction in number of airways. In agenesis the arteries were also disproportionately large. In renal agenesis pulmonary arterial wall thickness was less than normal fetal levels. This could reflect a difference in haemodynamic behaviour before birth or an effect on arterial growth other than that associated with size.

Pathogenesis of lung hypoplasia. In the past it has only been possible to discuss the nature and severity of the lung hypoplasia associated with renal disease in terms of the role of amniotic fluid, lung fluid, and urine production; and the explanations were not entirely satisfactory.

In a retrospective study of 31 cases with renal anomalies Perlman and Levin (1974) found that 21 of these had oligohydramnios associated with hypoplastic lungs; the remainder with normal lungs had normal amniotic fluid.

In 2 cases of prolonged leakage of amniotic fluid reported by Perlman *et al.* (1976) the number of alveoli present at birth was the normal expected number at the time of onset of the leakage, suggesting that no further development occurred after fluid was withdrawn. It is pressure of the uterine wall, due to lack of fluid, which is likely to produce the Potter facies and the limb malformations but restriction of the thoracic cavity is unlikely to cause lung hypoplasia as the chest wall is never badly deformed in renal agenesis.

Recent experiments by Alcorn *et al.* (1977) have shown that drainage of the fluid from fetal lamb lungs during development *in utero* leads to a decrease in lung volume and lung tissue with abnormal maturation of the alveolar wall. The reduction in peripheral lung tissue in the present series may be due to excessive drainage of fluid from the lung in the absence of amniotic fluid. In the lamb the lung normally contributes about one-third of the amniotic fluid (Strang, 1977).

The contribution of the kidney to the liquor is important only relatively late in pregnancy (Saunders and Rhodes, 1973). Findings in the present series suggest that because the airway number implied an interference with growth before 16 weeks' gestation, oligohydramnios is unlikely to be the sole cause of lung hypoplasia.

The absence of the kidneys in the cases of agenesis may have a direct but unidentified effect on the lungs. Experimental nephrectomy in fetal lambs has an effect on subsequent fetal growth with a reduction in the glycogen reserves of the liver (Thorburn, 1974). Unfortunately, the lungs were not studied in these experiments.

During fetal development the kidney appears to be an important source of proline: it contains an arginase that influences proline production through an arginine ornithine proline cycle. Clemmons (1977) injected nephrotoxins into chick embryos at various times and followed the effect on the production and metabolism of ^{14}C labelled proline. Decreased ability to metabolise proline was associated with decreased collagen formation. Because it grows actively during the times chosen, he studied the morphological state of the lung, and found it became hypoplastic with sparse mesenchyme. The association of a renal defect and lung hypoplasia can now be interpreted in the language of biochemical and metabolic processes and this offers new ways of investigating the interaction between the kidney and the lung.

In renal dysplasia, lung volume and alveolar and airway size and number are reduced but the cases vary in their severity. In renal agenesis these changes are more pronounced and are associated in addition with disproportionately larger airways and arteries, the latter also having thinner walls. The fact that more severe hypoplasia is seen with renal agenesis than with dysplasia may reflect either a greater reduction in available proline or a difference in the time-table of interference.

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Cows' milk protein-sensitive enteropathy

An important contributing cause of secondary sugar intolerance in young infants with acute infective enteritis

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SUMMARY The effect of cows' milk protein (CMP) on the mucosal disaccharidases was investigated in 23 infants with acute infective enteritis. Jejunal biopsies performed before and after cows' milk provocation were subjected to histological examination and to mucosal disaccharidase enzyme (lactase, sucrase, and maltase) analyses. After milk challenge, changes in mucosal histology were observed in 18 infants, in 17 of them the levels of all 3 mucosal disaccharidases were much reduced. 10 of these infants developed diarrhoea and, in 6, the stools were positive for reducing sugar. It is concluded that CMP has a deleterious effect on the jejunal mucosa of young infants recovering from infective enteritis, so that in the management of young infants with sugar intolerance secondary to infective enteritis, CMP and lactose should be excluded from the diet.

Secondary sugar intolerance is a well recognised and common complication of acute infective enteritis (AIE) in young infants (Burke, *et al.*, 1965; Lifshitz *et al.*, 1971; Chandrasekaran *et al.*, 1975). The intolerance appears to be due to depletion of mucosal sugar-splitting enzymes secondary to damage to the small bowel mucosa caused by the primary infective agent (Weijers and Van de Kamer, 1962; Barnes and Townley, 1973). Exclusion of this sugar, however, does not always affect the diarrhoea. Recently cows' milk protein sensitive enteropathy (CMPSE) was shown to be an important factor prolonging diarrhoea in young infants with AIE (Iyngkaran *et al.*, 1978a). The present study was undertaken to determine the effect of cows' milk protein (CMP) on the intestinal oligosaccharidases in infants recovering from AIE.

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Materials and methods

23 infants under age 12 months presenting with the clinical features of AIE, admitted to the Department of Paediatrics, University Hospital, Kuala Lumpur between March 1976 and March 1978 were studied. Investigations on admission included examination of the stools under the light and electron microscope for *Giardia lamblia* and virus, stool cultures for bacterial pathogens, and testing of stools for sugar by the method of Kerry and Anderson (1964).

After appropriate correction of fluid and electrolyte imbalances the infants were started on a formula free of CMP—such as Prosobee, Nutramigen, or Pregistimil (Mead Johnson). All infants remained in hospital until their stools were normal, they were feeding well, and were gaining weight. They were then discharged home, usually within 2 weeks of admission, the mothers being supplied with the appropriate CMP-free formula and instructed not to offer any other milk without first consulting us. About 6 or 8 weeks later the infants were readmitted for further study.

Further study.

Low-lactose cows' milk provocation test*

In most infants 'Al 110' (Nestlé) or 'Lactolac V' (Co-operatieve Condensfabriek Friesland, Holland) was used. If no reaction occurred after an initial feeding of 5 ml, the volume was doubled hourly for the first 4 hours and subsequently 3-hourly until daily fluid requirements were met.

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* < 0.07% Lactose after reconstitution.

Testing of stools
If diarrhoea occurred stools were tested for reducing sugar.

Pathogens
In all infants attempts were made to isolate parasitic, bacterial, and viral pathogens from the stools by culture and by examining stools under the light and electron microscope 12 to 24 hours before and 12 to 24 hours after milk challenge.

Jejunal biopsy
A proximal jejunal biopsy specimen taken with the Watson paediatric capsule just distal to the duodenojejunal junction was examined under dissecting microscope. The specimen was divided into three—one portion was fixed in gluteraldehyde for light and electron microscope studies, the 2nd was used for oligosaccharide enzyme determinations, and the 3rd for immunofluoresence studies. In addition a mucosal imprint was performed to detect *G. lamblia* (Kamath and Murugasu, 1974). Jejunal biopsies were performed (a) prechallenge, immediately before CMP challenge, and (b) postchallenge, 24 hours after the introduction of cows' milk, irrespective of the presence or absence of symptoms. Biopsies were graded by a method described previously (Iyngkaran *et al.*, 1978b).

Assay of intestinal disaccharidases. Portions of jejunal biopsy material were homogenised and incubated with the various disaccharidase substrates as described by Dahlquist (1968). Aliquots of the incubation were assayed for glucose at timed intervals for up to 2 hours using a Glucose Analyzer (Beckman Instruments Inc., Calif. 92634, USA). Disaccharidase activities are reported as µmol of disaccharide hydrolysed/min at 37°C per gram wet weight of tissue.

In 4 infants protein (micro-Kjeldahl method for total protein, Bauer *et al.*, 1974) and enzyme estimations were performed simultaneously. The enzyme levels in these 4 infants were expressed both as per gram wet weight of tissue and per gram protein. The percentage drop in the enzyme levels after milk provocation by either method was almost identical. In the other 19 cases the enzyme levels were expressed as per gram wet weight of tissue.

Results

Initial assessment. The 23 infants comprised 5 Malays, 11 Chinese, and 7 Indians (13 boys and 10 girls). The mean age at admission was 70 days (3–300). The mean duration of diarrhoea was 3·6 days (1–12). Dehydration was present in 13 infants, abdominal distension in 7, anal excoriation in 8, and oral thrush in 7. Interestingly, 8 infants had neonatal jaundice and 5 developed diarrhoea while on phototherapy in a ward with noninfectious patients.

At initial admission stools were positive for sugar in 13 infants; in the other 10, stools were not tested (Table 2). Food poisoning *Salmonella* was isolated from the stools of 4 infants, *Escherichia coli* from 2, and *Shigella* from one.

Assessment at milk challenge. At the time of readmission for milk challenge all the infants were clinically well and registered satisfactory weight gains: 3 were still excreting *Salmonella* and 4 were extreting *E. coli.* These organisms could not have been introduced during challenge studies as stools collected immediately before and after challenge were positive for the same organisms.

Biopsy findings (histological and enzymological). The prechallenge biopsy was normal in 17 infants and mildly abnormal in 6. The infants could be categorised into 4 groups according to the clinical and histological response to CMP after challenge.

Group A. Infants with histological and clinical relapse, symptoms appearing within 24 hours (8 infants)
There was significant depression in the levels of all 3 disaccharidases. In 6 infants with diarrhoea, stools were tested and found to be positive for reducing sugar.

Group B. Infants with histological and clinical relapse but symptoms appearing at 3 and 14 days after milk provocation (2 infants)
There was significant enzyme depression in both infants.

Exclusion of CMP produced prompt cessation of symptoms in infants of groups A and B.

Group C. Histological relapse but no clinical symptoms (8 infants)
Disaccharidase levels were depressed in 7 of the 8 infants. Two have been lost to follow-up. The remaining 6 were thriving well on a CMP formula, when last seen 1 to 24 months after milk provocation but, in 2, initial weight gains were suboptimal.

Group D. No histological or clinical relapse (5 infants)
Although some variability in the pre- and postchallenge enzyme values were observed, there was no consistent fall in enzyme levels as in the 17 patients in groups A, B, and C.

Although the reduction in the mean levels of the disaccharidases in group A was significantly greater than those in group C the levels in individual cases overlapped greatly.

The clinical features, Clinitest results, stool isolates, histological findings, and enzyme values in the 4 groups are summarised in Tables 1 to 5.

Table 1 *Clinical features of 23 infants with acute enteritis*

	Group A *n=8*	*Group B* *n=2*	*Group C* *n=8*	*Group D* *n=5*
Age (days) at initial admission				
Mean	24	3, 49	40	207
Range	(3–42)		(5–135)	(135–300)
Male/female	4/4	0/2	6/2	3/2
Ethnic group				
Malay	2	–	2	1
Chinese	3	1	4	3
Indian	3	1	2	1
Weight at initial admission (kg)				
Mean	3	3	3	6·5
Range	(2–4·65)	(2, 4)	(1·83–6·3)	(5–8·2)
Age (days) at onset of diarrhoea				
Mean	21	22·5	36	204
Range	(4–35)	(3, 42)	(4–130)	(131–288)
Duration of diarrhoea				
Mean	2·8	4	4·3	3·5
Range	(1–3)	(1, 7)	(1–12)	(2–6)

Table 2 *Stool Clinitest results in 23 infants with acute enteritis at initial illness and after cows' milk challenge*

Group	*Clinitest*	*Initial illness*	*Postchallenge*
A	Positive	6	6
	Not done	2	2
	Total	8	8
B	Positive	2	–
	Not done	–	2
	Total	2	2
C	Positive	5	
	Not done	3	No diarrhoea
	Total	8	
D	Positive	2	
	Not done	3	No diarrhoea
	Total	5	

Table 3 *Stool isolates from 23 infants with acute enteritis during initial illness and milk provocation*

Group	*Pathogens*	*Initial illness*	*Pre- and postchallenge*
A	*Salmonella*	2	2
B	–	–	–
C	*E. coli*	2	3
D	*E. coli*	1	1
	Salmonella	2	1
	Shigella	1	–

Table 4 *Jejunal biopsy findings* in 23 infants with acute enteritis before and after cows' milk provocation*

Group	*Prechallenge*	*Postchallenge*			
		Normal	*Mild VA*	*Moderate VA*	*Severe VA*
A	Normal 6 (1·2)	–	1 (7)	2 (8·8)	3 (12·5)
	Mild VA 2 (4)	–	–	1 (9)	1 (12)
	Total 8	–			
B	Mild VA 2 (4)	–	–	2 (11)	–
C	Normal 7 (0·8)	–	6 (6·1)	1 (9·5)	–
	Mild VA 1 (4)	–	–	1 (11)	–
	Total 8				
D	Normal 4 (1·8)	4 (1·7)	–	–	–
	Mild VA 1 (6)	–	1 (5·5)	–	–
	Total 5				

VA=Villous atrophy.

*Figures in parenthesis denote mean score; normal histology=0–3, mild VA=4–7, moderate VA=8–11, severe VA >11.

Discussion

Secondary sugar intolerance complicating AIE in young infants appears to be due to depletion of the disaccharidases secondary to mucosal damage caused by the primary infective agent (Lifshitz *et al.*, 1971; Barnes and Townley, 1973). In the management of such infants the sugar is identified and excluded from the diet. Dietary manipulation becomes more difficult in those infants who do not improve with this simple approach. It often culminates in some being placed on an oral carbohydrate-free formula (Sirolac, CF1, Nestlé), with glucose given intraveneously (Lifshitz *et al.*, 1970; Walker-Smith, *et al.*, 1973). However, a certain proportion of these infants continue to have diarrhoea despite the total exclusion of carbohydrate from the oral feeds. Harrison *et al.* (1976) suggested a possible association between CMPSE, lactose intolerance, and AIE. Recently, studies in young infants with AIE showed that the feeding of CMP during recovery damages the small bowel mucosa (Iyngkaran *et al.*, 1978a). Such damage could in itself perpetuate the diarrhoea or, by depleting the mucosal disaccharidases, contribute to the problem of secondary sugar intolerance.

18 of 23 infants with AIE in the present series had CMPSE by the criteria of Iyngkaran *et al.* (1978b). In 17 of these infants significant depression of the disaccharidases occurred after provocation with CMP. 10 of these infants had diarrhoea, 8 within 24 hours and 2, on days 3 and 14, after milk provocation. Stools were positive for reducing sugars in 6 infants. As the CMP formulae used in the provocation studies were glucose based and had negligible amounts of lactose, it is suggested that CMP not only impairs digestion and absorption of disaccharides but also of monosaccharides.

Table 5 *Disaccharidase levels, mean (and range)* in 23 infants with acute enteritis before and after cows' milk provocation*

Group	*No. of cases*	*Disaccharidase*	*Prechallenge*	*Postchallenge*	*Percentage change‡*
A	8	Lactase	3·3 (0·7–5·8)	0·5 (0·1–1·4)	85 (76–97)
		Sucrase	4 (1·7–6·4)	1·6 (0·4–2·8)	69 (36–92)
		Maltase	18 (3·1–27)	5·7 (0–14·6)	68 (44–100)
B	2	Lactase	2·8 (2·7, 2·9)	1·1 (0, 2·3)	60 (100, 20)
		Sucrase	4 (4, 4)	2·7 (1·6, 3·9)	31 (60, 2)
		Maltase	23·6 (20, 27·2)	7·3 (1·9, 13·8)	70 (90, 49)
C†	8	Lactase	2·8 (0·9–6·1)	1·3 (0·7–2·4)	54 (5–90)
		Sucrase	4·3 (1·8–7·2)	2·3 (1·0–3·7)	46 (0–86)
		Maltase	14·9 (4·4–24·5)	12·1 (4·1–23·4)	19 (0–73)
D	5	Lactase	2·3 (1·4–3·4)	2·4 (1·4–4·1)	−4·0 (−20 to 0)
		Sucrase	3·0 (1·4–5·1)	2·9 (1·7–4·1)	2·0 (−20 to 20)
		Maltase	12·1 (7·7–17·3)	13·1 (7·9–17·1)	−2·5 (−20 to 12)

*µmol/min per g wet weight tissue.

†Included in this group is one infant who had histological changes without significant alterations in any of the disaccharidases.

‡Percentage change $= \frac{(\text{prechallenge} - \text{postchallenge})}{\text{Prechallenge}} \times 100$; positive values indicate decrease and negative values increase over the prechallenge.

Not all 17 infants with histological changes and enzyme depression developed symptoms. Similar observations have been made in coeliac disease (MacDonald *et al.*, 1965). The severity and extent of damage, the amount of lactose, the amount and type of CMP in the diet, the ability of the infants to digest the protein and render it harmless, their ability to mount an appropriate immunological reaction, and the presence of intercurrent enteric infections are some factors that may determine whether or not symptoms manifest in them.

The immunological mechanisms for the exclusion of foreign protein such as CMP by the intestinal mucosa are age dependent (Taylor *et al.*, 1973; Walker, 1975). In young infants this problem may become exaggerated in any situation such as AIE where damage to the intestinal mucosa further increases the permeability to foreign protein. The free passage of foreign antigen across the mucosa could then sensitise the intestinal mucosa to the protein. Subsequent re-exposure to the protein could then result in an immunological reaction at the mucosal level; this may lead to secondary damage of the small bowel mucosa and the attendant consequences of diarrhoea, secondary sugar intolerance, malabsorption, and failure to thrive (Harrison *et al.*, 1976; Iyngkaran *et al.*, 1978a). Therefore in the management of young infants with sugar intolerance secondary to AIE, a lactose- and CMP-free formula should be used and continued for some weeks after recovery.

The deleterious effects of CMP in infants with AIE and secondary sugar intolerance have gone unrecognised in the past because most of the lactose-free milk preparations such as Sobee, Prosobee, Nutramigen, and Pregestimil (Mead Johnson) are also free of CMP. Clearly more studies are needed to confirm these findings and the magnitude of the problem. This would then pave the way for a review of some of the current concepts of secondary sugar intolerance complicating AIE and enable the formulation of a more rational approach to treatment.

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Prognostic factors in acute meningococcaemia

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SUMMARY During a meningococcal (group A) epidemic, 47 Nigerian children with acute meningococcaemia without meningitis were studied. Their mortality rate was 43% compared with 8% during the whole epidemic. Those presenting with coma and shock had a mortality of 93%, but without shock or coma mortality was only 6%. Coma or shock occurring alone carried an intermediate prognosis. The outcome correlated with initial serum antigen titre, but not with the serum levels of endotoxin, cortisol, or fibrin degradation products. Chloramphenicol was as effective as penicillin. A predictor of expected mortality, based on serum antigen titre and the presence of coma or shock, may allow new forms of treatment to be assessed.

Acute meningococcaemia still has a high mortality during African epidemics (Lapeyssonie, 1963), as in the rest of the world, especially in those patients without meningitis. Mortality rates in such patients were as high as 60% with Flexner's intrathecal antiserum therapy during the 1930s. Subsequent use of antibiotics, corticosteroids (May, 1960), heparin (Niklasson, *et al.*, 1972), digoxin, and IV fluid regimens (Murray *et al.*, 1974; Cahalane and Waters, 1975) has not lowered the mortality. Edwards (1971) showed that high titres of meningococcal capsular antigen are found in the serum during the fulminant form of the infection, and suggested that a threshold level, beyond which disease is irreversible, might exist. The value of other prognostic indices —such as hypotension, duration of purpura, CSF counts, and peripheral blood counts—has been discussed (Stiehm and Damrosch, 1966; Niklasson *et al.*, 1971). We studied some of these factors and also serum levels of endotoxin and cortisol, and fibrin degradation products (FDP) in an homogenous group of Nigerian children suffering from acute group A meningococcaemia, during a large short-lived outbreak. A report on the general features of the epidemic, with its overall mortality of 8%, is in preparation.

Patients and methods

Patients. 47 children with acute fevers, petechial haemorrhages, and CSFs clear to the naked eye were chosen from a total of 530 paediatric admissions for meningococcal disease. During the 3-month epidemic, this group served to define clinically a syndrome of 'acute meningococcaemia without meningitis'. Diagnosis was proved in 37 either by the detection of group A antigen by countercurrent immunoelectrophoresis (Edwards, 1971), or by a positive culture from blood or CSF. Two of the 10 unproved cases died before they could be investigated. Four others had siblings with proved meningococcal meningitis, and the remaining 4 lived close to known cases.

Age ranged from 1½ to 12 years (mean 5·9) and 26 (55%) were boys. The highest CSF WBC was $250/\text{mm}^3$ ($0\cdot250\times10^9/\text{l}$) and 80% of patients had counts lower than $5/\text{mm}^3$ ($0\cdot005\times10^9/\text{l}$).

In most patients continuous monitoring of BP, central venous pressures (CVPs), ECGs, and rectal and skin temperatures was maintained.

Treatment. Either benzylpenicillin (1 megaunit 6-hourly IV if patient under 4 years, up to 3 megaunits 6-hourly if over 8 years), or chloramphenicol (25 mg/kg 6-hourly IV) was given.

In any patient with shock (defined as systolic BP <3rd centile for an American population, i.e. <75 mmHg under 4 years, and <85 mmHg over 4 years), IV dextran 70 was given as quickly as possible until CVP and BP were restored.

At first digoxin was given to patients with pulmonary oedema, but later in the epidemic, this treatment was given to all hypotensive patients.

Prednisolone (50 mg 6-hourly IV) was given to some patients late in the epidemic.

Laboratory methods. Studies were performed on encoded specimens of serum and CSF taken at

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presentation. Endotoxin assay was used for samples collected in endotoxin-free bottles (after swabbing the skin with iodine) and preserved deep-frozen. With the Limulus test and chloroform-extraction (Levin *et al.*, 1972), the lysate used (Marine Biologicals) could detect a standard endotoxin diluted in serum at a level of 2 ng/ml. A semiquantitative assay of FDP was performed by the slide latex agglutination test (Burroughs-Wellcome). Serum cortisol was assayed by competitive protein-binding (Murphy *et al.*, 1963).

Because of local mores, there were no necropsies.

Statistics. Unproved cases are not included in the results. Nonparametric tests were used if appropriate, and methods are quoted in each case.

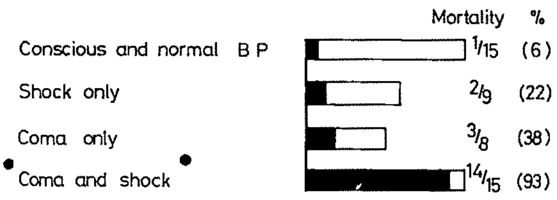
Results

Mortality. 20 of the 47 clinically diagnosed cases died. Of the 37 proved cases, 18 (49%) died. All survivors were completely cured. Most (55%) deaths occurred in the first 4 hours in hospital, and 80% during the first 12 hours.

Clinical presentation and prognosis. Of the various presenting features, shock and coma (absence of co-ordinated response to pain) were the most decisive prognostically (Fig. 1). If a child presented with a normal BP and was conscious his chances of recovery were good. Nearly all children presenting with both coma and shock died. Shock or coma carried an intermediate risk.

Length of history did not correlate with mortality: 80% had been ill for <24 hours, and 40% for <12 hours. The proportion dying in each group was the same.

All 47 children had conjunctival petechiae easily seen, and 20 had purpura less obvious on their dark skin. Those with skin purpura had a higher mortality than those without (50% compared with 37%), but this was not statistically significant.



(Solid areas indicate deaths; $P<0{\cdot}001$ $\chi^2=24$)

Fig. 1 *Mortality and presenting syndrome.*

The height of fever did not relate to mortality, but a rectal temperature exceeding skin temperature by 3°C or more (reflecting the vasoconstricting shock) did.

Clinical progress. Some patients, although initially well, deteriorated during the first 8 hours of observation, while others made a progressive recovery (this difference was shown to relate to serum antigen titre). The mode of deterioration was characteristic; rate and depth of respiration increased, conscious level fell, and purpura extended as CVP fell to zero. Heart rate rose to over 150/min as BP fell, often suddenly and to unrecordably low levels. Although BP and CVP rose with dextran, the coma and hyperventilation usually persisted, with tetany and features strongly suggesting pulmonary oedema (widespread rales and copious frothy blood-tinged sputum). The CVP, usually held below 10 cm, never exceeded 14 cm, while ECG showed sinus tachycardia (150–180/min), S–T segment changes (usually digitalis effect), and an unchanging normal axis. Arrythmia was rare: in one patient a few ventricular ectopics were seen and, in one other, a wandering pacemaker. Bleeding from mucosae or venepuncture sites occurred in only the comatose and deeply shocked patients, all of whom had received dextran.

Treatment. Penicillin and chloramphenicol were equally effective. In patients in whom the diagnosis was proved, 7 out of 14 given chloramphenicol and 11 out of 22 given penicillin died. The two groups were evenly matched for age, presenting features, and serum antigen titre.

Dextran 70 was almost always effective in restoring CVP and BP; usually 20 ml/kg was required. In the absence of controls, a reduction in mortality cannot be shown.

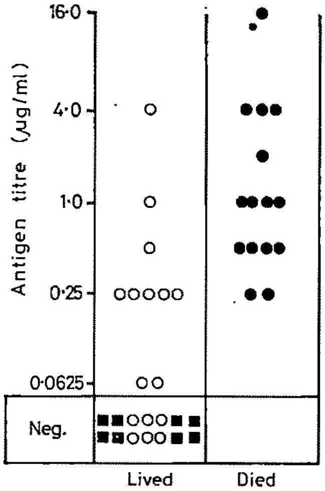
Digoxin had no discernible effect clinically, but ECG showed S–T effect without obvious toxicity.

Prednisolone, given to only 6 patients, had no apparent effect. Phenoxybenzamine was given to 2 patients in unresponsive shock. One died after an hour: in the other, despite rapid resolution of shock and pulmonary oedema, coma persisted until death 4 weeks later.

Laboratory findings.

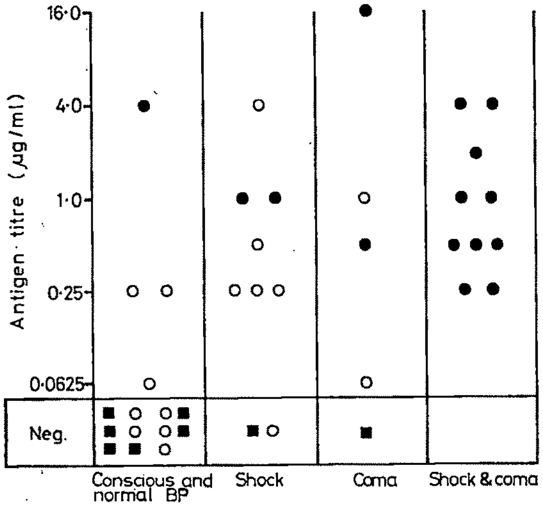
Serum antigen

The presence of group A antigen in serum correlated with mortality; 17 (57%) out of 30 antigen-positive cases died while none of the 6 antigen-negative (but proved) cases died ($P<0{\cdot}025$ Fisher's exact test). The titre of antigen also correlated with mortality (Fig. 2; $P<0{\cdot}001$ Mann-Whitney test).



■ = Not bacteriologically proved.

Fig. 2 *Mortality and serum antigen titre.*



○ = Lived, ● = died, ■ not bacteriologically proved.

Fig. 3 *Mortality, presenting syndrome, and antigen.*

All patients with an antigen titre $<0·25$ μg/ml survived, but there was no threshold beyond which death was inevitable. If serum antigen titres are compared with the presenting features (Fig. 3), it is obvious that higher titres relate to more severe disease ($P<0·025$ Kruskall-Wallis test).

Endotoxin

Assays on sera of 7 healthy controls gave one positive result (i.e. >2 ng/ml). Six out of 16 patients' sera had positive results. There was no relation between a positive result and either clinical severity or mortality. Death occurred in one out of 6 children with a positive result, and in 2 out of 10 with a negative one.

Fibrin degradation products

Initial serum titres showed no correlation with clinical severity, bleeding complications, or mortality. Three out of 7 patients with FDP <10 μg/ml died as did one out of 3 with a level >40 μg/ml.

Serum cortisol

Levels are shown in Fig. 4. All are high (normal range 100–500 nmol/l; 3·6–18 μg/100 ml) with no significant difference in mean level between those who lived (708±SD 109) and those who died (724±SD 273). The levels did not correlate with clinical syndrome, antigen titre, FDP, or endotoxin levels.

Cerebrospinal fluid

Antigen was detected in 8 patients' CSF, 4 of whom had cell counts below $5/mm^3$ ($0·005\times10^9/l$). CSF culture was positive in 10 patients, 3 of whom had cell counts lower than $5/mm^3$. CSF endotoxin assay was positive in 5 out of 15 patients. None of these findings related to clinical features, serum findings, or mortality.

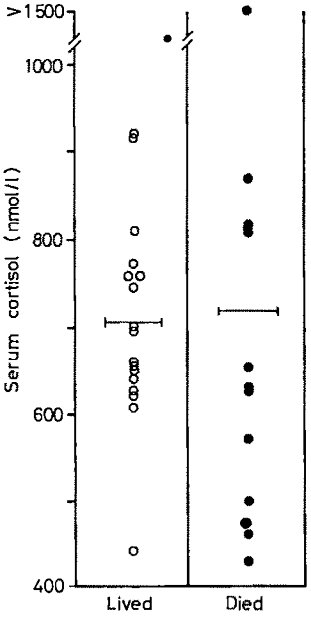


Fig. 4 *Mortality and serum cortisol.*

Discussion

The identification of poor-risk meningococcaemic patients on the clinical findings of petechiae, fever, and clear CSF is imperative during epidemics. Diagnosis may quickly be confirmed by finding group A specific antigen in the blood, and bedside prognostication is improved by antigen titration. Ideas on the mechanism and management of the ensuing catastrophe continually change, so the important facets are considered in the light of our findings.

Banks (1948) described 4 forms of acute meningococcaemia: the ordinary, the 'adrenal', the encephalitic, and the 'mixed' form, corresponding to our clinical categories. His stress on brain injury, supported by necropsy findings, has received too little attention in other studies. This was a crucial prognostic factor in our patients, and was evident as coma regardless of BP, pulmonary oedema without a raised CVP, and tetanic hyperventilation. It was not related to meningitis in the sense of a cell exudate, although in some patients a positive culture or antigen was found in an acellular CSF—a long-known fact (Glasscock, 1935). The shock itself may be of central nervous origin (Ducker and Simmons, 1968), mediated by pulmonary (Udhoji *et al.*, 1963) or splanchnic (May, 1960) pooling, rather than by cardiotoxicity (Levin and Painter, 1966; Hardman and Earle, 1969). Hypotension is preceded by hyperventilation, failing consciousness, and a fall in venous return without actual change in blood volume (May, 1960). The full-blown syndrome with frank pulmonary oedema was seen in several patients at presentation, and therefore cannot be attributed to excessive IV infusion. In our patients digitalisation was of doubtful benefit, but dextran restored BP and CVP. Although α-blockers and β-stimulants hold promise for correcting the circulatory changes, in our 2 patients so treated coma persisted until death. There was no evidence that the encephalitis responded to corticosteroids, but its reversal in 6 patients not given corticosteroids was encouraging. 'Suprarenal apoplexy' (Waterhouse, 1911) is an unlikely cause of death as shown by the high cortisol levels, clinical findings, and ineffectiveness of corticosteroid treatment.

Endotoxaemia as detected in our patients was also of no prognostic significance; perhaps the Limulus test lacks clinical value (Stumacher *et al.*, 1973), or endotoxin is not the central issue after all (Kass *et al.*, 1973).

Disseminated intravascular coagulation (DIC), although clearly demonstrated in acute meningococcaemia, may likewise be unimportant or perhaps it is unresponsive to heparin. Initial FDP level did not predict progress. Of 70 heparin-treated cases in 15 reports (Niklasson *et al.*, 1972) 38 patients died. A controlled trial of heparin (Manios *et al.*, 1971) did not show significant benefit. The dextran used in our patients may have countered DIC and improved microcirculation, but it was intended primarily as a plasma expander.

High serum antigen levels at presentation, while not invariably fatal, point strongly to a poor prognosis. This free antigen may be a quantitative marker of live organisms, their dead products, or of an ineffective immune neutralisation and/or phagocytosis. In meningococcal meningitis, CSF antigen level has been correlated with brain damage and higher mortality, and serum antigen positivity with higher mortality (Whittle *et al.*, 1976). Further study to define the role of antigen is needed.

Long experience of sulphonamides (May, 1960) and penicillin, and the effectiveness of chloramphenicol in our patients, suggest that the choice between a bactericidal or bacteriostatic drug is immaterial, provided that the organism is sensitive. It seems that fulminant meningococcaemia is caused by unlimited multiplication of unneutralised bacteria which disrupt leucocytes, and activate the complement (Greenwood *et al.*, 1976) and coagulation pathways; perhaps crucially they have direct toxic effects (although possibly not endotoxic) on the brain. Fulminant disease is present in only a small proportion of the population during meningococcal epidemics. The susceptible may have low levels of circulating antimeningococcal antibody (Goldschneider *et al.*, 1969), or a defect of antibody response (Whittle *et al.*, 1976), although polymorph dysfunction cannot be ruled out. Since a few dramatic recoveries have been reported using IV antibacterial (Glasscock, 1935) or antitoxic sera (Hoyne, 1935), and modern treatment persistently fails to reduce mortality, we intend to try the combination of IV penicillin and IV antiserum in severe cases. A simple prognostic index, based on the presenting features of coma, shock, and serum antigen level should help to assess such treatment.

I wish to thank Drs H. C. Whittle and B. M. Greenwood for their help and guidance; Professors R. H. Dobbs and M. K. Haggie, the staff and students of the paediatric department: Mr M. Damisah for his expert laboratory work; Professor I. D. P. Wootton, Dr K. Mashiter, and Miss S. Baker of the Royal Postgraduate Medical School for the cortisol assay.

Addendum

Since submitting this paper, we have found highly significant depressions of serum antithrombin III levels correlated with prognosis; this may help to explain the apparent unresponsiveness of the condition to heparin.

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Aortic arch interruption presenting with absence of all limb pulses

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SUMMARY Three patients with aortic arch anomalies presented with severe heart failure, acidaemia, and poor or absent upper and lower limb pulses. Prominent carotid arterial pulsations were detected which distinguished the condition clinically from aortic atresia. In 2 patients with a left aortic arch, interruption was distal to the left common carotid artery and there was an aberrant right subclavian. In the 3rd patient with a right aortic arch, interruption was distal to the right common carotid and there was an aberrant left subclavian artery. By dilating the narrowed ductus, prostaglandin E2 infusion corrected the acidosis. Successful surgical correction was achieved in one patient by direct anastomosis of descending aorta to ascending aorta and the base of the left common carotid artery.

Complete interruption of the aortic arch is a rare congenital anomaly which normally presents in infancy with heart failure and acidaemia (Fishman *et al.*, 1976). There is almost always a ventricular septal defect and persistence of the ductus arteriosus (Roberts *et al.*, 1962). When the interruption is between the left common carotid artery and the left subclavian artery (type B of Celoria and Patton (1959)), the descending aorta is supplied from the pulmonary artery via the ductus arteriosus and also by retrograde flow from the left vertebral artery, which also supplies the left subclavian artery.

When an infant presents with cyanotic congenital heart disease, heart failure, acidaemia, and reduced or absent upper and lower limb pulses the diagnosis of aortic atresia is likely. With type B interruption of the aortic arch, when the right subclavian artery arises aberrantly from the descending aorta, and the ductus arteriosus constricts (Fig. 1), a similar clinical picture is found. In this case, however, there will be normal or bounding carotid pulses. This is now a surgically correctable lesion and hence the importance of its recognition. We report 2 cases that presented in this manner, and a further similar patient with a right-sided aorta, grossly hypoplastic arch distal to the right common carotid, and aberrant left subclavian artery.

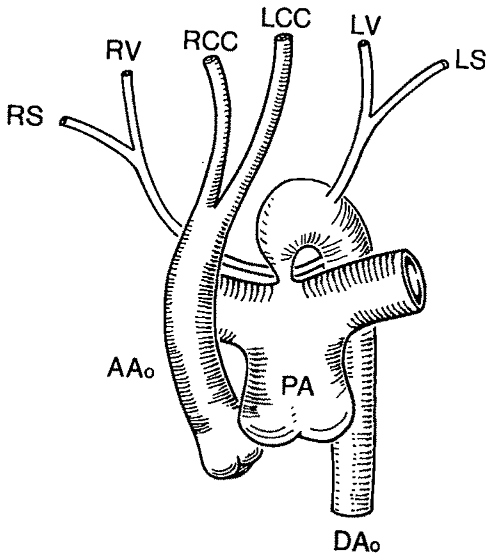

Fig. 1 *The ascending aorta (AAo) gives off only the right common carotid artery (RCC) and the left common carotid artery (LCC). The pulmonary artery (PA) connects with the descending aorta (DAo) through a constricted ductus arteriosus. The left subclavian (LS) and right subclavian (RS) arteries arise from the descending aorta and give off the right vertebral (RV) and left vertebral (LV) arteries.*

Case reports

Case 1. A Caucasian baby boy, normal delivery, born at 39 weeks' gestation with a birthweight of

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2·9 kg. On day 2 a murmur was noted and at that time all the peripheral pulses were normal. The next day he became cyanosed, tachypnoeic, and was found to be in heart failure with no pulses palpable in the arms or legs.

He was transferred to the Wessex Cardiothoracic Centre where he was found to be severely tachypnoeic, sweating profusely, with 3 cm hepatomegaly. There were no pulses palpable in the limbs but bounding carotid pulses were present bilaterally. There was a much increased parasternal impulse and on auscultation there was an ejection click, soft short ejection systolic murmur, and a single second sound. The ECG suggested right ventricular hypertrophy and the left ventricular potentials were well seen. The chest *x*-ray showed a large heart with plethoric lung fields.

The echocardiogram showed the presence of 2 atrioventricular valves, 2 ventricles and 2 arterial valves, the anterior of which had midsystolic closure suggesting that it was the pulmonary valve.

Cardiac catheterisation proved the diagnosis of complete interruption of the aortic arch between the left common carotid artery and the left subclavian artery with the right subclavian artery arising aberrantly from the descending aorta (Fig. 1). Injection into the ascending aorta showed delayed retrograde filling of both vertebral arteries, and hence both subclavian arteries and the descending aorta. There was also a ventricular septal defect and a persistent ductus arteriosus. When the catheter was passed from the pulmonary artery to the descending aorta there was loss of pressure waveform and injection of contrast showed very slow clearing from the descending aorta. There was also a small left-to-right shunt at atrial level which proved to be due to a secundum atrial septal defect.

Surgical correction was performed the same day using profound hypothermia, and total circulatory arrest at 18°C (Barratt-Boyes *et al.*, 1971). The technique was virtually the same as that used by Trusler and Izukawa (1975). The descending aorta was dissected and mobilised and the duct divided from the pulmonary artery. The descending aorta, with most of the duct tissue removed, was then anastomosed to the ascending aorta and base of left common carotid artery. The pulmonary arteriotomy was closed and the right atrium incised. The atrial septal defect was closed directly, and the ventricular septal defect was closed through the tricuspid valve using a dacron patch. Total circulatory arrest lasted 68 min and the baby was taken off the ventilator and extubated 6 hours postoperatively. The postoperative course was complicated by intermittent collapse of the right upper lobe, but he left hospital 16 days after the operation.

He has not yet been reinvestigated but was well and thriving 3 months after surgery although he appears to have developed some aortic narrowing as the right arm and leg pulses are absent; however the left arm pulse is still present, but reduced.

Case 2. A Caucasian baby girl, normal delivery, born at 41 weeks. At 36 hours severe tachypnoea and cyanosis was noted and the baby was transferred to Brompton Hospital. On examination the child was extremely sick with absent limb pulses. Bounding temporal and carotid pulses were noted. Respiratory rate was 90/min. Examination revealed a split second sound with a loud pulmonary component and a grade 3/6 pan systolic murmur at the lower left sternal edge. Arterial P_{O_2} in 100% oxygen in the right radial artery was 17·3 kPa (130 mmHg), [H^+] 64 nmol/l (pH 7·19), base excess 19 mmol/l. Cardiac catheterisation showed a left-to-right shunt at ventricular level, equal ventricular pressures, and a pulmonary artery pressure of 52/27 mmHg. The catheter was advanced to the descending aorta where the systolic pressure was 15 mm lower, indicating constriction of the ductus. Left ventricular cineangiography showed a single high ventricular septal defect, filling of the ascending aorta and both common carotid arteries, but no opacification of the subclavian arteries or descending aorta (Fig. 2).

Injection into the left-sided descending aorta showed the left subclavian artery, the aberrant right subclavian, and the constricting ductus arteriosus (Fig. 3). Attempts at surgical correction were unsuccessful: the child died on the operating table.

The necropsy showed situs solitus, concordant atrioventricular and concordant ventriculo-arterial connections. The left-sided ascending aorta was a small channel giving rise only to right and left carotid arteries, confirming the angiographic diagnosis. The pulmonary artery was in continuity through a ductus with the descending aorta, from which arose the left and then right subclavian arteries. The right subclavian artery was posterior ascending behind the oesophagus. The arch was absent between left common carotid and ductus. The large ventricular septal defect resulted from backward displacement of the parietal insertion of the infundibular septum. The displaced infundibular septum caused severe narrowing of the left ventricular outflow tract, i.e. subvalvar aortic stenosis.

Case 3. A Caucasian baby boy, normal delivery, born at 40 weeks. At 24 hours severe tachypnoea and cyanosis was noted and the baby was admitted to the Brompton Hospital at 48 hours. The respiratory rate was 80/min. All limb pulses were barely palpable although temporal and carotid pulsations

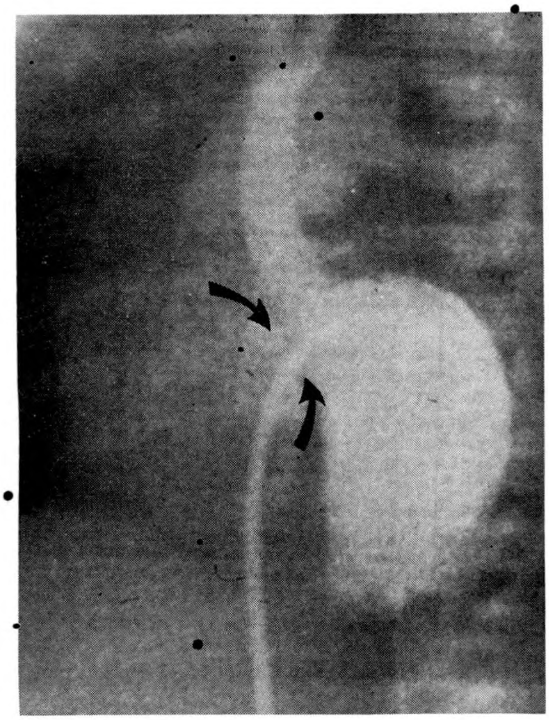

Fig. 2 *Left ventricular angiogram, lateral projection. The ascending aorta arises from the left ventricle and gives off the right and left common carotid arteries. The catheter is across the ventricular septal defect (between arrows) and there is faint left-to-right shunting of contrast across the ventricular septal defect.*

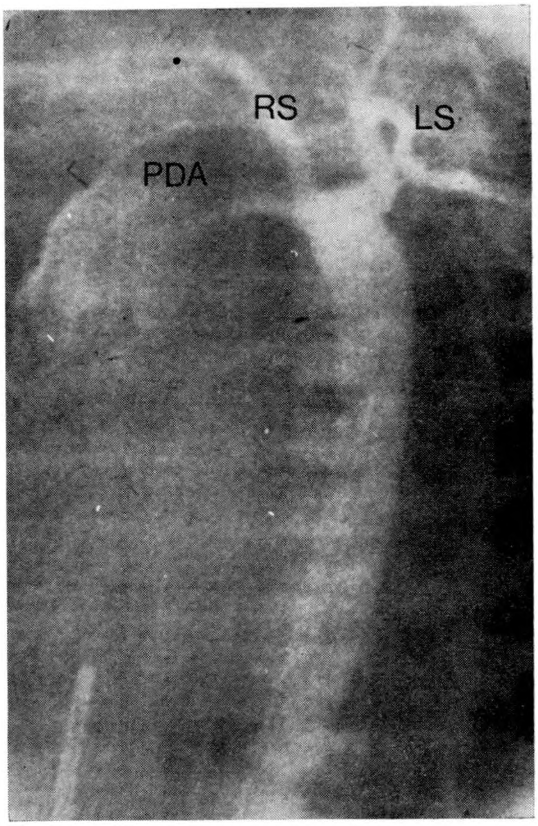

Fig. 3 *Injection of contrast into the descending aorta, lateral projection. The left subclavian (LS) and right subclavian (RS) arteries arise from it and the narrowed ductus arteriosus (PDA) fills.*

were felt. On asucultation there was a split second sound with a loud pulmonary component and a short systolic murmur at the lower left sternal edge. Arterial Po_2 in 100% oxygen was 8 kPa (60 mmHg), $[H^+]$ 64 nmol/l (pH 7·19), base excess 18 mmol/l. The ECG showed left ventricular hypertrophy with deeply inverted T-waves in the left chest leads.

Cardiac catheterisation showed a left-to-right shunt at ventricular level with equal ventricular pressures. The catheter was advanced through the ductus arteriosus into the descending aorta where the systolic pressure was 35 mm lower, indicating ductal constriction.

During and after cardiac catheterisation, acidosis became increasingly severe despite administration of IV bicarbonate. The child was considered too ill to undertake surgery at this stage. In order to improve systemic perfusion which was largely dependent on patency of the ductus, prostaglandin E2 infusion at the rate of 0·10 μg/kg per min was begun. This was delivered directly into the ductus from a catheter inserted via the umbilical artery. Within 15 min peripheral pulses became palpable and acidosis improved. The child remained anuric, however, and died on the operating table.

Necropsy showed situs solitus, normal connections, right-sided ascending aorta giving rise to both right and left common carotid arteries. The pulmonary artery was in continuity through a large ductus with a right-sided descending aorta from which arose the right and aberrant left subclavian arteries. The arch was grossly hypoplastic between the right common carotid and ductus. There was a large defect between the right ventricular infundibulum and the left ventricular outflow tract which appeared to be due to a complete absence of the infundibular septum.

Discussion

Patients with interruption of the aortic arch associated with a ventricular septal defect and persistent ductus arteriosus commonly present with heart failure in the first few days of life and 80% die in the first month. Therefore early recognition of the lesion is vital as surgical correction is possible (Tyson *et al.*, 1970; Barratt-Boyes *et al.*, 1972; Murphy *et al.*, 1973; Losman *et al.*, 1974; Trusler and Izukawa, 1975; Fishman *et al.*, 1976; Ventemiglia *et al.*, 1976; Monro *et al.*, 1977). Origin of the right subclavian artery from the descending aorta has been reported with interruption of a left aortic arch (Evans, 1933; Kleinermann *et al.*, 1958; Tabakin and Hanson, 1960, Zetterqvist, 1967; Morgan *et al.*, 1970; Van Praagh *et al.*, 1971; Subramanian, 1972; Kauff *et al.*, 1973; Murphy *et al.*, 1973; Trusler and Izukawa, 1975). We have been unable to find reports of an aberrant left subclavian artery associated with a hypoplastic right aortic arch.

At necropsy in infants with arch interruption the ductus arteriosus is usually widely patent with some wrinkling of the intima. Fournier and Zaidi (1960), Van Praagh *et al.* (1971), and Subramanian (1972) reported cases in which there had been significant narrowing of the ductus arteriosus. The combination of a right subclavian artery arising from the descending aorta and narrowing of the ductus arteriosus was present in the cases reported by Van Praagh *et al.* (1971), Subramanian (1972), and in 2 of our cases. In these, and in our 3rd case, a characteristic clinical picture of absent or markedly reduced limb pulses with bounding carotid artery pulsation was produced. This occurred because the subclavian arteries arose from the descending aorta, supplied by the narrowed ductus and by retrograde flow in the vertebral arteries. The detection of the large amplitude pulsation in the carotid arteries should suggest the clinical diagnosis. If carotid pulsation is not detected in an infant with heart failure, acidaemia, and absent limb pulses, aortic atresia—an inoperable lesion—may be mistakenly diagnosed. We have seen 2 patients with similar clinical findings caused by an intracranial arteriovenous fistula. The volume overload of the heart, due to the left-to-right intracranial shunt, caused heart failure and all the pulses were small except for the carotid arteries which were bounding as they supplied the arteriovenous fistula.

Infusion of prostaglandin E2 0·1 μg/kg per min has been used to dilate the ductus arteriosus in pulmonary atresia when pulmonary blood flow was dependent on its patency (Rudolph, 1977). Dilatation of the ductus by increasing lower limb flow helped to arrest the progressive acidosis accompanying ductal closure in one case. Aortic arch interruption is a further clinical situation where prostaglandin may be used. Mortality in this condition may thus be reduced as the infants' general condition at the start of surgery should be much improved by the adequate correction of acidosis.

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The following articles will appear in future issues of this journal:

Screening for cystic fibrosis in the newborn by meconium analysis. *H. C. Ryley, L. M. Neale, T. D. Brogan, and P. T. Bray.*

Medulloblastoma—a changing prognosis? *N. McIntosh.*

Foot length—a new and potentially useful measurement in the neonate. *D. K. James, E. H. Dryburgh, and M. L. Chiswick.*

Feeding the very low birthweight (1500 g and below) infant. One year's experience in an intensive care neonatal unit. *I. Beddis and S. McKenzie.*

A controlled trial of cyclophosphamide and azathioprine in Nigerian children with the nephrotic syndrome and poorly selective proteinuria. *A. Adeniyi, R. G. Hendrickse, and J. F. Soothill.*

Lomotil poisoning in children. *J. A. Curtis and K. M. Goel.*

Clinical evaluation and comparison of the Infrasonde, Arteriosonde, and mercury sphygmomanometer in measurement of blood pressure in children. *J. M. Savage, M. J. Dillon, and J. F. N. Taylor.*

Improved accuracy of continuous measurement of arterial oxygen tension in sick newborn infants: criteria for reading and recalibrating the electrode. *A. R. Wilkinson, R. H. Phibbs, and G. A. Gregory.*

Archives of Disease in Childhood, 1979, **54**, 54–58

Housing and mothering

Their effects upon the developmental levels of 3-year-old children

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SUMMARY The development of 200 3-year-old children was measured, using Gesell parameters of development. The levels of development were matched against the adequacy, or inadequacy, of maternal care and housing, the scales for which were derived from a questionnaire completed by the children's mothers. Housing was not found to affect the children's developmental levels, while the adequacy of maternal care was highly significantly related to satisfactory child development.

Be it castle or city slum, there is no place like home. Does research support this view? It is not easy to differentiate between the facilities of a home and the quality of care therein, and many research studies have failed to make this important distinction. The evidence that is available on the relative importance to a child of his mother and his home is somewhat conflicting. Several studies (Kaufman and Rosenblum, 1969; Spencer-Booth and Hinde, 1971a, b) have shown that monkeys who remained in their own 'homes' were distressed when their mothers were taken away, suggesting that the mother was more important than the home. Ross and Simpson (1971), on the other hand, found no intellectual retardation after the death of a parent if the child remained at home in familiar surroundings. When monkeys and children are removed from their homes they suffer distress (Edelston, 1943; Bakwin, 1949; Mac Keith, 1953; Robertson, 1958), but it is well known that this can be lessened if the mother accompanies the child to the new environment (Prugh *et al.*, 1953; Illingworth and Holt, 1955; Fagin, 1966).

A 'poor' home has been associated with poor educational achievement (Douglas, 1964; Department of Education and Science, 1967), backwardness (Burt, 1937), delinquency (Ferguson, 1966; West and Farrington, 1973), and psychiatric disorder (Rutter, 1976). However, the exact factors in the 'poor' homes which are important for the associations have not been defined.

Few studies have attempted to compare housing and maternal factors with measurable developmental levels in preschool children. But, if it were possible to separate housing conditions from parent care and to compare each of these factors with measured developmental parameters, comments could be made upon the relative importance of them on child development.

Present study

This cross-cultural study was made on 200 3-year-old children. 150 of them were born in the United Kingdom to 75 English parents and 75 West Indian parents. They were all living in the same district of south London, they came from similar social classes, and there were no significant differences in income levels. They have been described in detail elsewhere (Pollak, 1972). The remaining 50 children were living in North Carolina, USA and comprised 25 children born to white American parents and 25 born to negro American parents. These 50 children and their parents were in receipt of 'welfare'.

The 200 children were given 56 different paediatric development tests in their own homes in the presence of their mothers (or permanent mother figure). The tests, derived from Gesell (1954) and recorded (Pollak, 1972), were divided into sections to assess motor, personal-social, adaptive, and language parameters of development. The mothers filled in a questionnaire and from this, a scale of housing and maternal care was made.

Housing scale

1. The house was not multioccupied—i.e. not more than two families lived in the same house. If a flat or apartment, only one family occupied the rooms.
2. The main living room was large enough and had sufficient equipment to enable all the

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members of the family to sit down to a meal together.

3. The family had its own kitchen with running cold water.
4. The family had its own indoor water closet.
5. There was a usable bathroom for exclusive use of the family.
6. The 3-year-old child slept in his/her own cot or bed.
7. The parents and children had separate bedrooms.
8. Children of different sexes had different bedrooms.
9. There was a garden or play area in which the 3-year-old child could play.
10. The accommodation was self-contained with its own front door. Almost all the children in the USA study were in self-contained houses but they were isolated in lonely rural areas, so their point was scored if the nearest general store was within one mile.

Maternal care scale

1. The 3-year-old child was regularly put to bed by a parent.
2. The child had been given a present or treat for his/her birthday.
3. The mother stated that she spent at least half an hour each day playing with the child.
4. When the child misbehaved he/she was not beaten with a stick or belt, nor had he/she received more than one major punishment during the previous week. (A negative answer to both questions was necessary to qualify for the point.)
5. The mother knew the name of one current television programme for children and watched it with the child at least once a week. (Every household except one had a television set.)
6. During the 1½-hour interview the mother had appeared warm towards the child and had not shouted at him/her.
7. Three toys belonging to any child in the household had been shown to the examiner.
8. The mother was asked an open-ended question to describe her child in 5 different ways according to his/her character and behaviour. Two or more favourable replies scored one point. For example:

   Favourable

   'He's very loving, not selfish, got real good manners'.

   'She's more for her dad, but very loving and sweet'.

   'Oh, he's lovely. Very good most of the time but likes his own way—don't we all?'

   Unfavourable

   'Only gives you trouble. Only good when you belt him'.

   'Everything about him is bad. He just don't give you no mind'.

   'She is very rude. She is stubborn and lazy'.
9. If the mother went out to work she had made appropriate and firm arrangements for the child. In cases where the mother did not work but went out socially without the child, he/she was not left alone in the house or left casually in the charge of another child who was under age 14 years.
10. The child did not have to share his mother's attention with more than two other preschool children.
11. The mother was rated on a 4-point scale by the author for her understanding of and competence in carrying out the needs of the 3-year-old child. Among the factors considered, warmth, hostility towards the child, patience, and teaching skills had high priority.

The total possible score for housing was 10 and, for statistical purposes, a score of 6 or more was considered adequate, while 5 or less was inadequate.

For maternal care, the total possible score was 14. Eight or more was deemed adequate, while 7 or less was inadequate.

Table 1 *56 development tests*

Development	*Top possible score*
Motor	15
Personal-social	10
Adaptive	12
Language	14

The developmental levels of the children in these 4 parameters were then matched against the adequacy or inadequacy of the maternal care and housing scales.

Results

Housing. The development levels of the children were compared with the housing scores. In motor, personal-social, and adaptive development there was no significant difference between the scores when the housing was adequate or inadequate. Only in the case of the West Indian 3-year-old children did inadequate housing significantly lower the development score in language development (Table 2).

Table 2 *Developmental scores of 200 3-year-old children, matching adequate housing against inadequate housing*

Development	*Total*		*Inadequate housing*		*Adequate housing*		
	Mean score	*No. of children*	*Mean score*	*No. of children*	*Mean score*	*No. of children*	
Motor							
English	13·27	75	13·34	15	13·11	60	NS
West Indian	12·91	75	13·05	54	12·77	21	NS
American							
White	13·0	25	12·9	15	13·0	10	NS
Negro	12·5	25	13·0	5	12·2	20	NS
Personal-social							
English	8·9	75	8·84	15	8·94	60	NS
West Indian	7·0	75	7·15	54	6·85	21	NS
American							
White	8·4	25	8·3	15	8·5	10	NS
Negro	7·1	25	7·07	5	7·16	20	NS
Language							
English	11·9	75	11·64	15	12·12	60	NS
West Indian	3·85	75	3·47	54	4·23	21	P<0·05
American							
White	10·0	25	9·8	15	10·3	10	NS
Negro	5·24	25	5·07	5	5·16	20	NS
Adaptive							
English	10·2	75	9·97	15	10·43	60	NS
West Indian	3·5	75	3·82	54	3·16	21	NS
American							
White	8·6	25	9·1	15	8·2	10	NS
Negro	6·7	25	5·8	5	7·26	20	NS

Maternal care. A very different picture emerged when the children's developmental levels were compared with the maternal care scales. For all groups of children adaptive, language, and personal-social development were highly significantly related to the adequacy or inadequacy of maternal care. For the West Indian children motor development was also affected. In all cases, inadequate maternal care was related to a lower developmental score (Table 3).

Maternal care versus housing. For the children of this study the quality of maternal care was vital for their levels of development, but the adequacy of housing was not of similar importance (Table 4). Furthermore, the adequacy of maternal care was not found to be synonymous with adequacy of housing. A correlation graph (Figure) shows that the adequate mothers were not necessarily the mothers who were living in adequate housing.

Table 3 *Developmental scores of 200 3-year-old children, matching adequate maternal care against inadequate maternal care*

Development	*Total*		*Inadequate maternal care*		*Adequate maternal care*		*P*
	Mean score	*No. of children*	*Mean score*	*No. of children*	*Mean score*	*No. of children*	
Motor							
English	13·27	75	13·08	4	13·51	71	NS
West Indian	12·91	75	11·23	47	14·59	28	<0·05
American							
White	13·0	25	13·21	5	12·8	20	NS
Negro	12·5	25	12·0	12	13·07	13	NS
Personal-social							
English	8·9	75	7·9	4	9·86	71	<0·01
West Indian	7·0	75	5·93	47	8·07	28	<0·001
American							
White	8·4	25	7·5	5	9·3	20	<0·001
Negro	7·2	25	6·40	12	7·98	13	<0·01
Language							
English	11·9	75	10·6	4	13·2	71	<0·001
West Indian	3·85	75	2·84	47	4·86	28	<0·001
American							
White	11·0	25	9·32	5	12·68	20	<0·001
Negro	5·24	25	3·83	12	6·65	13	<0·001
Adaptive							
English	10·2	75	9·2	4	11·0	71	<0·01
West Indian	3·5	75	2·21	47	4·79	28	<0·001
American							
White	8·6	25	6·59	5	10·61	20	<0·001
Negro	6·7	25	4·68	12	8·71	13	<0·001

Table 4 *Developmental scales matched against the housing and maternal care scales*

	English	West Indian	American	
			White	Negro
Housing				
Motor	NS	NS	NS	NS
Personal-social	NS	NS	NS	NS
Language	NS	$P<0\cdot05$	NS	NS
Adaptive	NS	NS	NS	NS
Maternal care				
Motor	NS	P 0·05	NS	NS
Personal-social	$P<0\cdot01$	$P<0\cdot001$	$P<0\cdot001$	$P<0\cdot01$
Language	$P<0\cdot001$	$P<0\cdot001$	$P<0\cdot001$	$P<0\cdot001$
Adaptive	$P<0\cdot01$	$P<0\cdot001$	$P<0\cdot001$	$P<0\cdot001$

Discussion

It may appear a truism that a child's development is highly significantly related to his mother's love and care but is little affected by the circumstances and amenities of his home. However, this is not necessarily the case. A search in the literature for a study with which to compare these results fails to uncover any in which the various parameters of development are subjected to statistical relevance vis-à-vis maternal care and housing. Deprivation of maternal care has been associated with mental health (Bowlby, 1951), retarded language (Rutter and Mittler, 1972), and IQ (Haywood, 1967), but in no case with several parameters of development and housing factors.

It did not prove easy to devise the maternal care scales since the exact factors which contribute towards 'good' maternal care are not known. The factors which made up this scale were: care and attention (4 questions), warmth (2 questions), stimulation and interaction (4 questions), and the 4-point subjective rating. Because of the difficulty, direct answers given by the mother to direct questions put to her were used whenever possible. It was felt that as the questioner was the family doctor of all the UK mothers and children and was well known to them and the questions were asked close to other factual questions, the replies received were likely to be correct and many could be confirmed by observation.

In addition to the main conclusions of this study, it is possible to comment on some aspects of the different parameters of development. For example, there is some evidence to suggest that the genetic influence on motor development is strong (Illingworth, 1960; Geber and Dean, 1957, 1964; Pollak and Mitchell, 1974) and, because in this study motor development appears to be little influenced either by the housing or maternal care, both of which are environmental factors, the results could lend indirect support to this theory.

On the other hand, some workers who have been concerned with the environmental factors which affect child development have cited language development as an example of development which can be delayed by environmental factors. When opportunity to learn is meagre, language development can show retardation (Luria and Yudkovitch, 1959; Ausubel, 1963; Bernstein, 1965). This study supports this view but shows decisively that maternal care rather than housing is the significant variable. Clinical experience suggests that language development, alone, depends substantially on environmental factors.

Maternal care is found to have a significant effect upon adaptive development. Gesell and Armatruda (1947) have written 'The term adaptive behaviour is therefore a pertinent one to describe the category of

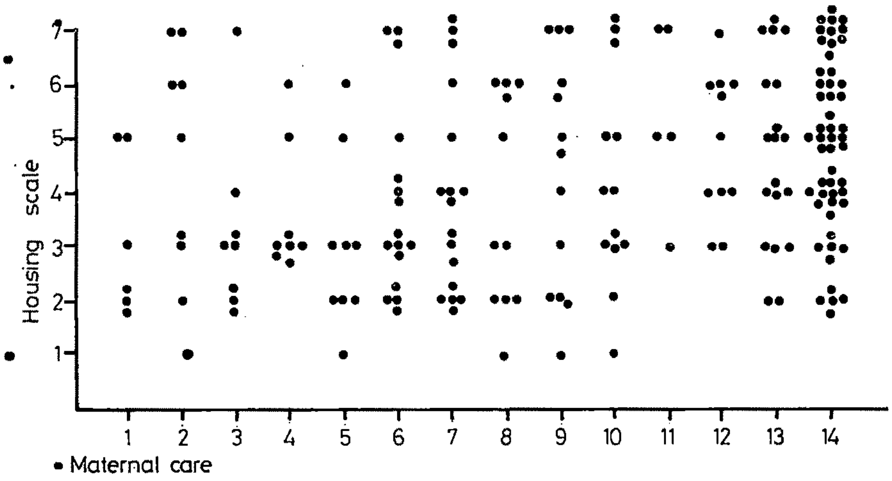

Figure *Housing v. maternal care.*

behaviour in young children which most correlates with what in older children is designated intelligence'. If one accepts this statement, then the results of this study suggest that inadequate mothering may carry a grave prognosis.

This research gives no information on the effect of housing upon mothers. Adequate shelter which contains the basic requirements for satisfactory housekeeping is a necessity for every mother and her family and we do not know whether a lack of these necessities caused depression and frustration in some mothers and thus affected, indirectly, her children. It is also not possible to comment on which factors in the maternal care scale were the most important.

The results of this paper put the onus of satisfactory development of the 3-year old firmly on the lap of maternal care and show that the adage 'There is no place like home' is only likely to be true when it contains an adequate mother.

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Conservative care of the newborn baby

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SUMMARY A method of managing ill and premature babies with little disturbance is described. The results of such care during 1969–76 compare favourably with those achieved by more intensive and active intervention.

Small or ill babies dislike being disturbed, and in the mid 1960s it seemed to me that intervention did harm as often as it did good. Here is described a way of leaving babies alone and its results.

Method

1. All babies are nursed prone and head up on an apnoea mattress. In this position the pharynx clears itself, the stomach is self winding, the lower oesophagus is protected by the gastric air bubble, and the brain drains uncongested.

2. The baby is never left naked but is covered at least by a towel napkin to reduce radiant heat loss. At night and on cold days, the nursery curtains are drawn.

3. A nasal tube is passed and feeding and watering begun within half an hour of admission. Feeds are given from outside the incubator without touching the baby. Babies fed only milk cannot satisfy their thirst and hunger independently as older children do. Most cope, but some become obese in an attempt to get enough water, or become oversalted, uraemic, and anorexic from a failure to do so. We therefore follow the example of other mammals by offering water 3 times a day to all babies. Those not sucking get their water down the tube in a volume equal to one of their milk feeds, with an increase if they are hot or uncomfortable. This is usually given as 10% glucose to the smaller babies as prophylaxis against hypoglycaemia, but water would probably be as good and perhaps safer, although we have had no trouble. Human milk expressed or from the breast, is used for the smaller babies and, if available, for the rest; but all milks seem well tolerated with supplementary water. For convenience we used pre-bottled milk when it became available. The quantity is increased from about 60 ml/kg per day on the 1st day to 120 ml/kg on the 3rd, up to 200 ml/kg by the 7th, depending on the state of the baby and the judgement of the sister.

4. At the first suspicion of respiratory difficulty an *x*-ray of the chest is taken, and acidaemia is anticipated and averted by adding sodium bicarbonate to the feed at a rate of $\frac{1}{2}$–1 mmol/h. The carbon dioxide formed leaves by the oesophagus, so the neutralisation is independent of lung function. The head up tilt is increased to 30° in the hope of reducing collapse of apical alveoli during expiration.

5. Blood glucose is checked by Dextrostix, at first every hour; and bilirubin as necessary by heel prick. No venous samples are taken except for culture if an infection is suspected. Nothing is given intravenously, except occasionally during initial resuscitation, or later for the correction of anaemia.

6. A stream of piped air, or air and oxygen, is directed from a funnel at the baby's face as a stimulus against apnoeic attacks. The concentration of oxygen is checked regularly, and enough given to prevent cyanosis.

7. Ventilators and positive pressure devices are not used, nor is phototherapy.

8. Isolation is kept to a minimum, and depends largely on the incubator and on hand washing. The nursery is open to mothers and relatives who are encouraged to help with the babies' care from the start. Masks and overshoes are not used, and gowns only for convenience; gloves are used for passing tubes.

9. During exchange transfusion, the umbilical catheter is sandwiched between two layers of adhesive film covering the abdomen, and the baby lies prone and unfettered in his usual position in the incubator.

Results

In 8 years, 911 babies under 2500 g were born. This was 6·1% of all births, and close to the national

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average of 6·3%. Of these, in 1974–76, 48·3% were between 2500 and 2250 g, 20·7% between 2250 and 2000 g, 19·1% between 2000 and 1500 g, 7·9% between 1500 and 1000 g, and 3·9% were under 1000 g. The corresponding figures for England and Wales for 1975 were 48·2, 22·8, 17·9, 7·4, and 3·5% respectively. Any larger baby about whom there was concern was also admitted to the nursery, and about one-third of all babies passed through if only for a few hours.

Hypothermia, hypoglycaemia, enterocolitis, pneumothorax, and bleeding and thrombotic complications were seldom met. Exchange transfusion was needed only for haemolytic disease, and there has been no late evidence of kernicterus. Babies with respiratory distress left undisturbed have done well with no late lung disorder. Apnoea has been severe only in babies later found at post-mortem examination to have cerebral haemorrhage from birth trauma. One severely retarded child is partially sighted and has retinal changes which may be related to ventilation with pure oxygen during half an hour's apnoea at birth; he did not need oxygen subsequently.

After discharge the babies were seen if necessary at a clinic held each week in the nursery, where the mothers were at ease and the nurses could see the results of their care. They did well. The few affected children were not those who had caused concern in the first weeks, and most had evidence of an intrauterine infection or some other handicapping condition. Some who had had unduly prolonged resuscitation at birth, and who needed tube feeding for a long time, remained severely retarded—the 'failed stillbirth' group for whom the answer is perhaps to limit initial ventilation for apnoea to 30 minutes or so, when there is evidence of profound intrapartum anoxia.

Death in the first week is the best defined measure of comparison; the number of deaths and births by weight is shown in Table 1, and the 3-year running average mortality in Table 2. All deaths are included whether they occurred in the delivery room, in the nursery, or after transfer to another hospital for surgery. Included in the table are the deaths in the first month for England and Wales by weight in 1975; and also deaths among 1017 babies of <2500 g admitted to six neighbouring nurseries in 1975, but it is likely that not all the larger babies are included in these figures.

Table 1 *First week deaths and number born, by year and weight*

Year	*Weight (g)*				
	1001–1500	*1501–2000*	*2001–2250*	*2251–2500*	*>2500*
1969	2/12	4/22	2/29	2/32	3/1735
1970	7/12	5/33	0/36	3/50	4/1775
1971	8/17	7/32	1/23	0/57	7/1763
1972	3/4	10/26	0/32	0/46	5/1725
1973	1/4	3/32	1/28	1/60	7/1770
1974	3/12	2/19	0/23	0/56	6/1795
1975	1/2	1/17	0/26	1/53	5/1700
1976	1/10	2/22	0/14	1/38	3/1750

Table 2 *First week mortality percentage by weight—3-year running average*

Years	*Weight (g)*				
	1001–1500	*1501–2000*	*2001–2250*	*2251–2500*	*>2500*
Salisbury					
1969–71	41	18	3	3	0·3
1970–72	55	24	1	2	0·3
1971–73	48	22	2	0·6	0·3
1972–74	35	19	1	0·6	0·3
1973–75	28	9	1	1	0·3
1974–76	21	9	0	1	0·3
England and Wales					
1975	45	13	4	2	
Wessex neighbours			*2001–2500*		
1975	46	14	3·3		

Among the smaller babies there was an initial rise followed by a steady fall in the mortality. As the care of the babies was unchanged, and the fall much steeper than the national trend, these changes are probably due to improvement in obstetric care. This was reflected in a corresponding fall in the number of babies who died after 20 minutes or more of apnoea at birth, or who had tentorial tears at post-mortem examination. Of the lethal deformities 19 were in babies >2500 g and 8 in smaller ones. Table 3 gives the cause of other deaths by year and weight. Table 4 shows the mortality of very small babies of <1000 g. This is high, but little different from that of babies born in University College Hospital, London as derived from the figures of Stewart *et al.* (1977), or from that reported by neighbouring nurseries.

Discussion

Different hospitals serve different populations, and reliable comparison between methods of care is difficult but should be attempted. The results of conservative treatment presented here seem no worse than those of more intensive care; and it may be that the method will be of use to other small hospitals in this country and overseas. The incidental benefits were considerable; nurses and doctors as well as babies got more rest, and it became practicable if not desirable to run the nursery with one trained and one assistant nurse or less per shift, with

Table 3 *Cause of death other than lethal deformities, prolonged intrapartum asphyxia, and tentorial tears*

Year	*Weight (g)*				
	1001–1500	*1501–2000*	*2001–2250*	*2251–2500*	*>2501*
Total born (1969–76)	73	203	211	392	14013
1969	None	*Klebsiella pneumoniae*	None	Cerebral bleed	*Pyocyaneus* septicaemia
1970	5 prematurity 1 cerebral bleed	1 cerebral bleed 1 respiratory distress (twin 2)	None	Cerebral bleed after prolonged rupture	None
1971	Prematurity	1 *Escherichia coli* 026 enteritis 1 cerebral bleed	Pierre Robin syndrome	None	Posterior fossa bleed
1972	Pulmonary haemorrhage	Respiratory distress after section for fetal distress	None	None	None
1973	Prolapsed cord	Posterior fossa bleed	None	Respiratory distress after section for fetal distress	1 cot death after section for prolapsed cord 1 viral pneumonia
1974	Prematurity	1 admitted moribund at 2 hours 1 intrapartum streptococcal septicaemia	None	None	None
1975	Admitted at 2 hours with hypothermia and adrenal bleeds	None	None	None	Septicaemia after operation for covered anus
1976	None	None	None	None	None

Table 4 *Very small babies*

	Born	*Died*	*Mortality (%)*	*Weight*
Salisbury (1969–76)	11	11	100	≤750 g
UCH, London (1966–75)	20	20	100	
England and Wales (1975)	1298	1029	79	≤1000 g
Wessex neighbours (1975)	31	23	74	
UCH, London (1966–70)	36	29	81	
(1971–75)	33	26	79	
Salisbury (1969–76)	21	16	76	751–1000 (all ages)
UCH, London (1966–75)	49	35	71	
Salisbury (1969–76)	21	16	76	751–1000 (<30 weeks)
UCH, London (1966–75)	40	32	80	

medical cover from a single doctor who also had responsibility for all the other paediatric work in the hospital.

It has been suggested that small babies should be transferred to regional centres. Table 4 shows that there has been little change in the mortality of very small babies in successive 5-year periods in one of the best of these; and that when babies of 30 weeks' gestation or more are removed the mortality differs little from the national average. Our experience suggests that improvement in perinatal mortality depends largely on the care of the mother and her baby before and during birth.

I am indebted to Sister Rowlands and the staff of Salisbury special care nursery for their help, and to neighbouring paediatricians for their kindness in providing figures.

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Plasma somatomedin activity in protein calorie malnutrition

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SUMMARY Somatomedin activity was assayed in the plasma of children suffering from protein calorie malnutrition by a bioassay using rat cartilage and expressed as sulphate uptake ratio. The sulphate uptake ratio was particularly reduced in kwashiorkor. In marasmus there was a slight reduction and the levels were still in the normal range. Plasma growth hormone (GH) levels were raised in kwashiorkor but were in the normal range in marasmus. Reduction in sulphate uptake ratio was observed only when plasma albumin levels were less than 2·5 g/100 ml (25 g/l). A rise in plasma GH was also observed but only below this threshold level.

Some of the actions of growth hormone (GH) on cartilage are believed to be mediated through GH-dependent serum factors—the somatomedins (Daughaday, 1971). The liver is one of the known sites of somatomedin generation that has been shown to be stimulated by GH (McConaghey, 1972).

Raised GH levels have been observed in kwashiorkor (Raghuramulu and Jaya Rao, 1974), a condition in which the concentrations of various proteins synthesised in the liver, including albumin, are markedly decreased. A lowered level of serum somatomedin may act as a feedback to stimulate excess production of GH in this condition. Plasma somatomedin is generally measured by bioassays, in which the uptake of either $Na_2{}^{35}SO_4$ or ^3H-thymidine by cartilage in the presence of serum is determined. To test whether any correlation exists between plasma GH levels and somatomedin activity in protein calorie malnutrition, the ability of serum from children suffering from such malnutrition to stimulate $Na_2{}^{35}SO_4$ uptake by rat cartilage was studied.

Patients and methods

Eight children suffering from kwashiorkor and 7 marasmic children were studied. They conformed to descriptions given earlier (Raghuramulu and Jaya Rao, 1974). Investigations were carried out immediately on admission to hospital and after 3 or 4 weeks of nutritional rehabilitation on diets which provided 200 kcal (0·836 MJ) and 4 g protein/kg daily. A sample of venous blood was obtained after an overnight fast, under resting conditions. Blood was collected under heparin, plasma separated, and stored at —20°C.

The bioassay was carried out as described by Yde (1968) using 21–27 day-old male albino rats, fasted for 48 hours before the assay. The cartilage pieces were however not subjected to acid hydrolysis but digested with papain (Alford *et al.*, 1972). The radioactivity in the hydrolysate was measured in a Packard liquid scintillation counter, using Bray's scintillating solution.

The assay was carried out by a symmetrical 4-point bioassay using both reference (pooled plasma from healthy adults) and test plasma at 10% (0·07 ml) and 20% (0·14 ml) of the total incubation volume (0·7 ml). Each concentration of the plasma was assayed in triplicate. Radioactivity was expressed per mg dry weight of the cartilage. The ratio of the radioactivity obtained with the test plasma to that obtained with the reference plasma was calculated and the average of the 6 observations was taken as the sulphate uptake ratio. Plasma samples of each child obtained on admission and after nutritional rehabilitation were assayed simultaneously, using the same rat to minimise interanimal variations.

In 7 independent assays normal plasma was used at 0, 2·5, 5, 7·5, 10, 12·5, 15, 17·5, 20% v/v concentrations and log dose response curves were constructed. The relationship was found to be linear up to a concentration of 20% v/v and the index of precision (λ) was 0·18 ± 0·020 (mean ± SE).

Plasma GH was estimated by the double antibody

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technique of Pennisi (1968), the materials used being similar to those described earlier (Raghuramulu and Jaya Rao, 1974). Plasma albumin was estimated by the biuret method (Wolfson *et al.*, 1948).

Results

The results of the study are presented in the Table. The mean sulphate uptake ratio in children suffering from kwashiorkor was significantly lower than that observed in normal children (P<0·001) and the values rose significantly after nutritional rehabilitation (P<0·01). The mean value in marasmic children was not different from that observed in normal children. However, there was a slight but significant increase after treatment (P<0·05).

The mean basal plasma GH level in children suffering from kwashiorkor was significantly higher than that observed in normal children (P<0·01). The levels came down significantly after nutritional rehabilitation (P<0·05). The mean level in marasmic children was not different from that observed in normal children and there was no change after treatment.

Correlations were tested between sulphate uptake ratio and plasma GH, between sulphate uptake ratio and plasma albumin, and between plasma GH and plasma albumin; both groups of children were tested separately before and after treatment. No positive correlations were obtained in any of the groups when tested individually. As the coefficients of correlation for both groups, before and after treatment, were not significantly different the entire data were combined for analysis. A significant correlation was obtained only between sulphate uptake ratio and plasma albumin concentration (r = 0·576, P<0·001, Figure).

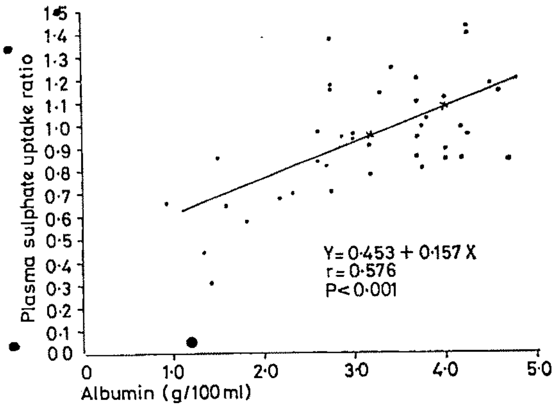

Figure *Relationship between plasma sulphate uptake ratio and plasma albumin level.*

Table *Plasma sulphate uptake ratio and GH levels in protein calorie malnutrition*

	Sulphate uptake ratio	*GH (ng/ml)*
Normal children (n = 11)	1·06 ± 0·072	8·4 ± 1·83
Kwashiorkor (n = 8)		
Before treatment	0·61 ± 0·059‡	30·8 ± 8·29†
After treatment	0·97 ± 0·085**	6·8 ± 2·18*
Marasmus (n = 7)		
Before treatment	0·97 ± 0·057	5·2 ± 0·82
After treatment	1·09 ± 0·056*	3·9 ± 1·06

Before treatment v. after treatment
* P<0·05, ** P<0·01.
Normal v. children with protein calorie malnutrition
† P<0·01, ‡ P<0·001.

Discussion

Data show that the plasma sulphate uptake ratio is lowered in kwashiorkor. As bioassay of somatomedin involves the stimulation of tissue sulphate uptake in the presence of plasma, the present study may be considered to indicate that plasma somatomedin activity may be lowered in kwashiorkor, an observation in line with that reported by Grant *et al.* (1973). Our data also show additionally that the sulphate uptake ratio is not altered in marasmus. The slight increase after treatment indicates that the reduction, if any, is only marginal. Van den Brande and Du Caju (1973) studied somatomedin activity in malnourished children and although they combined the data obtained from marasmic children with those from children with kwashiorkor, it would appear that both groups had low levels of activity. Their data also indicate the probable presence of a somatomedin inhibitor in the plasma of marasmic children. This was not tested in the present series. The normal sulphate uptake observed in marasmic children could probably be taken as evidence against the presence of such an inhibitor. The presence of an inhibitor in kwashiorkor however is not ruled out.

The finding that plasma GH levels are raised in kwashiorkor but normal in marasmus agrees with our earlier findings (Raghuramulu and Jaya Rao, 1974). There is a consensus regarding the high GH levels in kwashiorkor (Pimstone *et al.*, 1966; Beas *et al.*, 1971; Godard, 1973; Parra *et al.*, 1973; Suskind *et al.*, 1973) but observations on marasmus are discordant (Pimstone *et al.*, 1968; Beas *et al.*, 1971; Godard, 1973; Parra *et al.*, 1973; Suskind *et al.*, 1973). Circulating levels of several proteins known to be synthesised in the liver are markedly lowered in kwashiorkor (Gopalan, 1968). Liver is also one of the sites of somatomedin generation (McConaghey, 1972; Williams and Hughes, 1974). The lowering of somatomedin activity in kwashiorkor might therefore be due to its impaired synthesis, as was suggested by Grant *et al.* (1973).

It has been suggested that plasma amino-acid levels may determine plasma GH concentration in protein calorie malnutrition (Suskind *et al.*, 1973; Jaya Rao, 1974). The possibility that a decrease in somatomedin feedback, either on the pituitary or on the hypothalamus, could also stimulate excess GH production needs to be tested. The lack of correlation between the two substances at the outset precludes such a possibility. On the other hand, it was observed that in all children (except one) who had plasma albumin levels below 2·5 g/100 ml (25 g/l) the sulphate uptake ratio was below 0·7 (Figure). It has earlier been observed that plasma GH levels were raised only when the plasma albumin level fell below this concentration (Raghuramulu and Jaya Rao, 1974). The data of other workers (Pimstone *et al.*, 1968; Samuel and Deshpande, 1972; Lunn *et al.*, 1973) also support the latter observation. The results of the present study indicate that the reduction in sulphate uptake ratio as well as raised plasma GH levels are observed only below a certain threshold level of plasma albumin. They however, do not indicate whether somatomedin activity could be the primary determinant of the raised plasma GH levels in kwashiorkor.

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Isoniazid liver injury during chemoprophylaxis in children

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SUMMARY The incidence of INH-associated liver injury was evaluated in 239 children aged between 9 and 14 years, who were receiving 300 mg INH/day for tuberculosis prophylaxis. Serum SGOT and SGPT levels were determined before INH administration and at 4-weekly intervals thereafter. Levels of both enzymes were raised during the first 3 months of treatment in 18 (7·5%) children, while in 23 (9·6%) children either SGOT or SGPT exceeded normal levels (SGOT >40 units, SGPT >30 units). Only 2 (0·8%) children showed SGOT and SGPT values above 100 units and in them treatment with INH had to be discontinued. In all other children transaminases returned to normal during uninterrupted INH administration. It was noted also that transaminase values in children who did not exhibit a rise above normal, still had significantly higher levels during treatment compared with before. The findings of this study suggest that liver injury in children receiving INH for prophylaxis occurs more often than it had hitherto been believed but that it is usually mild and transient.

Isoniazid (INH) has been recognised as a cause of liver injury in patients receiving it. Several studies have shown there is an asymptomatic rise in the level of SGOT in 10–20% of adults given INH (Scharer and Smith, 1969; Bailey *et al.*, 1973; Mitchell *et al.*, 1975), although clinically overt hepatitis appears to be rare in such patients (Martin and Arthaud, 1970; Garibaldi *et al.*, 1972; Moss *et al.*, 1972; Black *et al.*, 1975; Mitchell *et al.*, 1976).

Most studies on the incidence of INH-associated liver dysfunction have been on adults. However Beaudry *et al.* (1974) estimated serum SGOT levels in children aged between 1 and 18 years and found that 6·8% of children receiving INH had higher levels of SGOT 2 months after the start of treatment. As treatment with INH is still used extensively in children, and because there is a lack of information on the incidence and clinical significance of liver injury during INH administration, this study was undertaken.

Materials and methods

The study group comprised 239 schoolchildren (128 boys and 111 girls) 9–14 years old (mean age 11·2). These children had been found to have a positive result to a tuberculin test during routine tests at elementary schools in Athens between November 1976 and March 1977, and they were therefore taking INH.

None of the children had active tuberculosis as shown in chest *x*-rays and by a normal ESR. Each child was given a month's supply of INH, to be taken as a single daily dose of 300 mg, and instructed to return to the clinic each month. Baseline determinations of SGOT and SGPT were obtained immediately before taking the INH and at monthly intervals thereafter.

Serum transaminase levels were determined using a modification of the Reitman and Frankel (1957) colorimetric method (kits from Dade Diagnostic, Inc.). Normal values for this method are 5–40 units for SGOT and 5–30 units for SGPT.

All children were examined for HB_sAg before INH administration. Any patient who subsequently showed an increase in the level of SGOT or SGPT in his or her blood sample was examined for HB_sAg by counterimmunoelectrophoresis and for infectious mononucleosis by the Monosticon test (Organon Teknika).

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Results

None of the 239 children had abnormal transaminase concentrations before taking INH.

In 41 (17·1%) of them a rise of at least one transaminase above the normal level was observed during the 12-week period after starting treatment. Two children who showed an increase in SGOT and SGPT but were found to have a positive result in the test for infectious mononucleosis, and 2 others who became HB$_s$Ag positive at the time that transaminase values increased were excluded from the analysis of the data. The increase in enzyme levels that took place during treatment with INH followed three different patterns (Table 1): 18 (7·5%) children showed an increase in both SGOT and SGPT levels. In another 18 children (Table 2) only SGOT increased above 40 units, and in 5 (2·1%) SGPT exceeded 30 units. A rise in the level of SGOT was noted in 36 (15%) children and in 23 (9·6%) children there was an increase in the SGPT level (Table 2).

In children in whom levels of SGOT and SGPT remained normal, an upward trend of the values during the first weeks of treatment was observed (Tables 3, 4). Although the difference between the mean values during each period of observation was small, the statistical analysis (paired *t* test) showed that it was highly significant (P<0·001).

The rise in the levels of enzymes took place during the first 2 months of treatment in most children (Table 4), but generally it was mild and transient. Only 2 (0·8%) children were found to have SGOT and SGPT values above 100 units and INH had to be discontinued. In the remaining 39 cases treatment was continued, but with close supervision and frequent monitoring. In these children the transaminases returned to normal levels within 4–8 weeks.

Table 1 *Children receiving INH who had SGOT values >40 units and SGPT values >30 units*

	No. of children	*% of total*
SGOT+SGPT	18	7·5
SGOT	18	7·5
SGPT	5	2·1
Total	41	17·1

Table 2 *Mean SGOT values in 203 children with SGOT levels <40 units during treatment with INH*

	Before treatment	*Weeks on INH*		
		4	*8*	*12*
Mean	20·7	23·8	24·3	23·0
SD	7·0	7·8	7·8	6·4
SEM	0·49	0·54	0·54	0·45

1, 2 t=4·1 P<0·001 1, 3 t=4·8 P<0·001
1, 4 t=3·3 P<0·001

Table 3 *Mean SGPT values in 216 children with levels <30 units during treatment with INH*

	Before treatment	*Weeks on INH*		
		4	*8*	*12*
Mean	9·3	11·7	11·6	11·8
SD	4·0	5·2	5·2	4·9
SEM	0·27	0·35	0·35	0·33

1, 2 t=5·5 P<0·001 1, 3 t=5·1 P<0·001
1, 4 t=5·9 P<0·001

Table 4 *Children showing raised transaminase values in relationship to duration of INH administration*

	No. of children	*Weeks on treatment*					
		4		*8*		*12*	
		No.	*(%)*	*No.*	*(%)*	*No.*	*(%)*
SGOT	36	19	(53)	11	(30)	6	(17)
SGPT	23	13	(57)	8	(35)	2	(8)

Discussion

These data confirm earlier observations—made mainly in adults—that some patients receiving INH may develop high levels of serum transaminase without overt signs of liver disease (Scharer and Smith, 1969; Bailey *et al.*, 1973; Mitchell *et al.*, 1975).

In most previous studies patients were monitored for liver injury by determination of one transaminase. The incidence of abnormal SGOT values in these studies ranged from 10 to 20% of the patients taking the drug (Byrd *et al.*, 1972; Bailey *et al.*, 1973; Mitchell *et al.*, 1976).

In a similar study in 178 adolescents SGPT values became abnormally high in 10% of patients within 10 weeks of taking INH (Litt *et al.*, 1976).

Until recently no data of hepatic function had been reported in children receiving INH for prophylaxis and the *ad hoc* Committee on Isoniazid and Liver Disease in Atlanta, Georgia, USA, stated in a report issued in 1971 that 'isoniazid-associated liver disease does not appear to occur in children.' Since then reports have suggested that severe hepatic injury (Rudoy *et al.*, 1973) or even death (Vanderhoof and Ament, 1976) might occur in children taking INH. Beaudry *et al.* (1974) who studied SGOT levels in 369 children on INH prophylaxis reported increased levels of SGOT in 6·8% of them.

In the present study in which both SGOT and SGPT concentrations were monitored, a rise above normal values for both enzymes was detected in 18 (7·5%) out of the 239 children. In addition 23 (9·6%) more children showed an increase either in SGOT or SGPT, during the period of observation (Table 1). The incidence of 17·1% for children with raised transaminase values is significantly higher than the 6·8% incidence reported by Beaudry *et al.* (1974). The reason for this difference is not clear and it could be due to differences in the techniques used to determine enzyme levels. It is evident that it is difficult to compare data from different studies. More studies using strict criteria are needed.

Another interesting finding in the present study was that higher values of SGOT and SGPT were noted in most patients compared with levels before treatment (Tables 2, 3). Although this difference was small, the statistical analysis (paired *t* test) showed that it was highly significant ($P<0\cdot001$). This finding, not reported by others, suggests that liver injury is more common than is shown by an increase in the level of enzymes. It has been suggested that the degree of liver injury may be greater if INH is given at the same time as enzyme-inducing drugs such as rifampicin (Pessayre *et al.*, 1977).

It is apparent from previous studies, and confirmed by this one, that most patients with subclinical hepatic damage recover completely while continuing on INH, and do not progress to overt hepatitis. The fact that in the present study only 2 patients had a rise of SGOT and SGPT above 100 units and had to stop taking INH, while 39 children were able to continue to take it and their SGOT and SGPT levels returned to normal, shows that although INH prophylaxis is rarely associated with clinically significant liver injury, transaminase levels should be monitored in the first month of treatment to detect patients who might be susceptible to liver damage.

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Short reports

Delayed diagnosis of congenital anal stenosis

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SUMMARY The consequences of a delayed diagnosis of congenital anal stenosis in 11 children are described. A plea is made for proper anal examination in the newborn, the technique for which is described.

Congenital abnormalities of the anus are easily detected. Nevertheless the diagnosis is sometimes missed, with serious consequences for the child. Between 1970 and the end of 1977, 11 children with minor congenital anal abnormalities, in whom the diagnosis was initially missed, were seen on one surgical firm at this hospital (Table 1).

After diagnosis and initial treatment intravenous urography was performed on each child; bilateral hydronephrosis and hydroureter due to posterior urethral valves were present in one patient (Case 11). The urograms were normal in all the others.

Treatment and results

All the children were treated surgically. Nine required anoplasty followed by dilatations. In the remaining 2 limited courses of anal dilatation were sufficient. The results are summarised as either 'satisfactory' (Table 2) or 'unsatisfactory' (Table 3). The 'unsatisfactory' group all have persistent constipation with occasional faecal impaction; all require laxatives and, between them to date, they have had 17 hospital admissions. Four have had contrast enemas confirming the presence of a persistent megarectum. Two cases may be quoted.

Table 1 *Details of 11 cases of anal stenosis*

Case	*Sex*	*Age (months)*	*Presenting complaint*	*Anomaly*
1	M	42	Faecal incontinence	Covered anus and skin tags
2	M	5	Constipation	Anal stenosis
3	F	5	Constipation; abdominal mass	Anal stenosis
4	F	6	Constipation	Anal stenosis
5	F	7	Abdominal mass	Anal membrane; stenosis and skin tags
6	F	5	Abdominal distension; diarrhoea	Anal stenosis
7	F	4	Constipation	Covered anus
8	F	4	Rectal bleeding	Anal stenosis and skin tags
9	M	1	Oseophageal atresia	Anal stenosis
10	M	1½	Abdominal distension	Covered anus
11	M	1	Constipation	Covered anus

Case 1. A boy aged 3½ years was referred because of overflow rectal incontinence. On inspection of the anus a congenital abnormality was obvious (Fig. 1). The obstructing rigid hood of skin was excised (Fig. 2).

Case 6. A 5-month-old baby girl presented with abdominal distension and diarrhoea. Before being seen by us a barium enema had been performed but the anus had not been examined. The enema showed an appearance compatible with Hirschsprung's

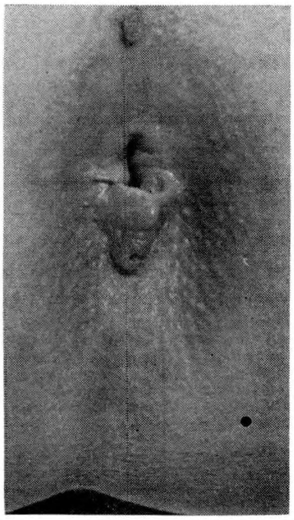

Fig. 1 *Anal abnormality is obvious on inspection.*

disease (Fig. 3) and it was for this reason that a surgical opinion was sought. The anus looked normal but on attempting digital examination a tight stenosis at the dentate line was detected. Rectal biopsy was normal.

Table 2 *'Satisfactory' group*

Case	*Age at presentation (months)*	*Functional result*	*Duration of treatment needed (months)*
7	4	Normal	2
8	4	Normal	4
9	1	Normal	3
10	1½	Normal	7
11	1	Normal	3

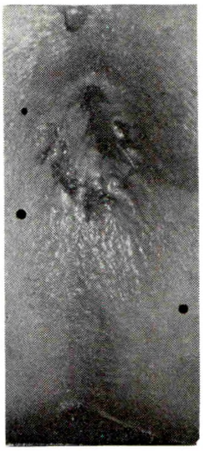

Fig. 2 *Obstructing skin has been excised.*

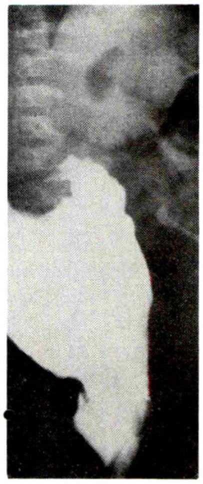

Fig. 3 *Barium enema (Case 6). Appearance is compatible with Hirschsprung's disease.*

Table 3 *'Unsatisfactory' group*

Case	*Age at presentation (months)*	*Functional result*	*Duration of treatment to date (months)*
1	42	Unsatisfactory	12
2	5	Unsatisfactory	54
3	5	Unsatisfactory	11
4	6	Unsatisfactory	18
5	7	Unsatisfactory	21
6	5	Unsatisfactory	12 then lost to follow-up

Discussion

Although classed by us as a minor abnormality, anal stenosis, if neglected, becomes a major one requiring prolonged surgical treatment and supervision. The longer the stenosis is untreated the more severely affected the rectum becomes so that in the worst cases the rectum becomes grossly distended, insensitive, and apparently aperistaltic (Fig. 4). This constitutes a severe disability, the treatment is prolonged and major surgery may be needed. Our results (Tables 2 and 3) and the experience of others (Partridge and Gough, 1961; Stephens and Smith, 1971; Taylor *et al.*, 1973) show that the sooner the diagnosis is made and effective treatment instituted, the better the prognosis.

In 3 of these children simple inspection of the anus was sufficient to reveal an abnormality requiring closer scrutiny. However, the anus can look perfectly

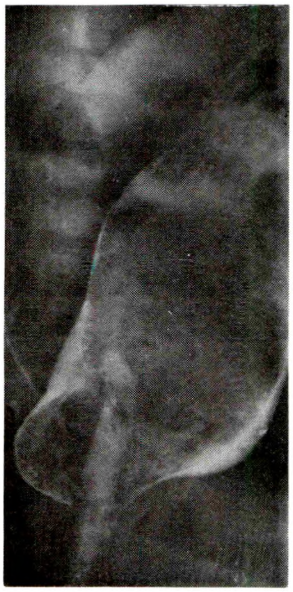

Fig. 4 *Barium enema in Case 5 showing huge megarectum full of faeces.*

normal and yet be severely stenosed. The normal passage of meconium and stools is not a reliable guide to the state of the anus, as a stenosed anus will often allow meconium and the soft stool of the newborn to escape. Similarly a rectal thermometer can usually be easily introduced into the rectum in these cases.

The technique of anal examination in the newborn is easy. The anus should first be inspected and then palpated. The little finger, well lubricated, should be used. The finger is inserted into the anus, pad first, very slowly and very gently. The normal anus will stretch as this is done and in most cases a little finger can enter the rectum. However, the examiner's finger may be too big or, as in the case of a very small baby, it may obviously be unwise to over dilate and injure the anus. With practice all degrees of anal stenosis can be excluded without the finger tip entering the rectum. During the palpation two points in particular should be noted. Firstly, the absolute size of the anus. More important than this is the suppleness or otherwise of the canal. A rigid anal canal is an abnormal one.

The anus is easily amenable to examination in the newborn. If there is any doubt that there is even a slight element of stenosis an expert surgical opinion should be urgently obtained.

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Acute anuric renal failure in an infant with systemic candidiasis

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SUMMARY We report a newborn baby who presented with acute anuric renal failure resulting from systemic candidiasis. The predisposing factors and diagnostic features are examined.

Although the newborn baby is susceptible to infection and mucocutaneous thrush is common, systemic candidiasis is rare. When it does occur in babies it usually causes osteomyelitis, arthritis, and meningitis. Renal failure is not a recognised feature.

Case history

A boy was born in August 1977 at 29 weeks' gestation, birthweight 1.430 kg. Respiratory distress syndrome developed and he required ventilation for 23 days. A blood culture taken at 2 days grew *Staphylococcus aureus* and he was given ampicillin and cloxacillin. Subsequently he received courses of gentamicin and carbenicillin.

He was fed intravenously from 3 to 22 days of age via silastic cannulae. These were placed in various veins, including the left long saphenous. At 21 days the long saphenous site became infected and blood cultures grew *Candida albicans*. The cannula was therefore removed. Five days later 3 ml pus was drained from the abscess; Gram's stain showed yeast cells and mycelial elements; cultures produced a profuse growth of *C. albicans*. He was given benzylpenicillin, streptomycin, and lincomycin from 25 to 30 days and the abscess healed. Thereafter he made good progress and for 5 weeks he fed normally and gained weight. Five blood cultures during this period were sterile.

When he was 64 days old he suddenly became anuric and was transferred to Leeds. There was no urine in the bladder on catheterisation. An intravenous urogram showed nephrograms of 2 normal size kidneys which failed to excrete dye into the renal pelvis. A cystogram was normal; there was no urethral obstruction and no vesico ureteric reflux. After a week of anuria blood tests showed: Hb 6.4 g/dl, WBC 14.8 × 10^9/l (14 800/mm^3) (75%

neutrophils, 24% lymphocytes), normal platelets, and no evidence of disseminated intravascular coagulation; plasma urea 20 mmol/l (120 mg/100ml), K 6.3 mmol/l.

In order to find out if recovery was likely, and if dialysis was justified, the baby was given an open renal biospy on day 71. Macroscopically the kidney looked mildly oedematous. The renal pelvis felt normal and contained no obstructing mass. On microscopical examination the renal tissue appeared viable, so peritoneal dialysis was begun the next day and continued for 3 days. Further study of the sections showed *Candida* within the kidney. Intravenous 5-fluorocytosine therapy was begun with 200 mg/kg per day initially. Blood levels a thousand times the minimum inhibitory concentration (MIC) of the *Candida* were obtained (MIC 0·15 mg/dl). Two days later he began to pass urine which on microscopical examination contained budding yeast cells and hyphae (Fig. 1).

During this time he also had extensive bronchopneumonia and required further ventilation. The blood culture grew *C. albicans*. There was clinical improvement, the pneumonia resolved and he continued to pass urine. The blood cultures remained positive although the *Candida* in the blood was allegedly sensitive to fluorocytosine. For a while clinical improvement was maintained, but he deteriorated suddenly to die at 86 days of septicaemia.

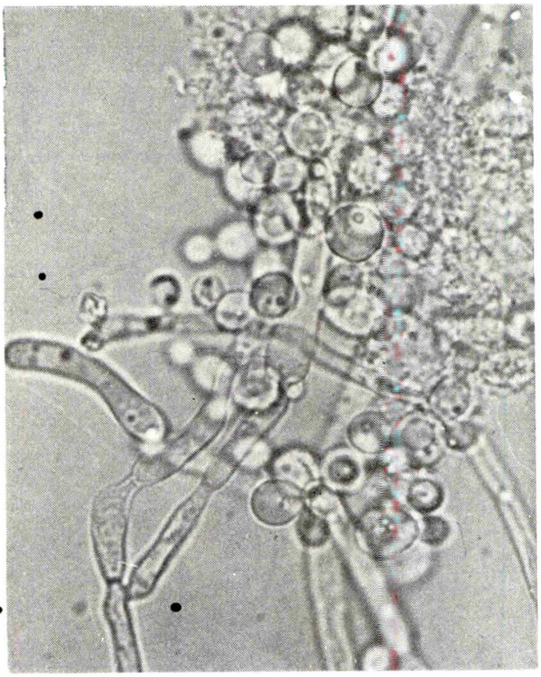

Fig. 1 *Unstained urine HP × 100. Budding yeast cells and hyphae.*

Renal biopsy (Fig. 2)

A total of 65 glomeruli was seen per section, none being hyalinised or scarred. There was a marked dilatation of Bowman's space in 20%. The tubules were preserved but showed marked epithelial, cloudy swelling, and focal dilatation. At two points there were small foci of necrosis involving tubules and interstitium, accompanied by mixed inflammatory cell infiltration (Fig. 2). Along the side of the biopsy, but not within the areas of necrosis, were abundant fungal filaments which were PAS- and Gram-positive and which stained positively with Grocott's stain for fungi (Fig. 1). These filaments had the morphology of *C. albicans*. It was considered that the biopsy revealed viable renal tissue which showed toxic and reactive changes, probably due to renal infection with *C. albicans*.

Necropsy

The right kidney. This had become a pyonephrosis and was about 4 times normal size. There was a pronounced reduction in renal tissue in some areas and the lower lobe was infarcted.

The left kidney. This was a little enlarged. Small white abscesses were scattered throughout the parenchyma and there were areas of *Candida* in the interstitium. There was a large abscess, 1 cm across, occupying the lower lobe.

Discussion

It is unusual for an apparently healthy baby to develop acute renal failure. The total anuria suggested urinary tract obstruction, but that was excluded by the urogram and cystogram. Intrinsic renal disease was the only alternative. Acute tubular necrosis or renal venous thromboses were unlikely because of the immediate good health of the baby. Despite intensive investigation the cause was not found until *Candida* was identified in the renal biopsy tissue. It is possible that the anuria was a result of intrarenal obstruction by fungal growth in the renal tubules. Alternatively an 'acute pyelonephritis' shutdown might have occurred from fungal infection.

Systemic candidiasis in infants usually presents as osteomyelitis, arthritis, and meningitis (Businco *et al.*, 1977). In most cases the infant is premature and receiving antibiotics. A vein has usually been catheterised for intravenous feeding (Boeckman and

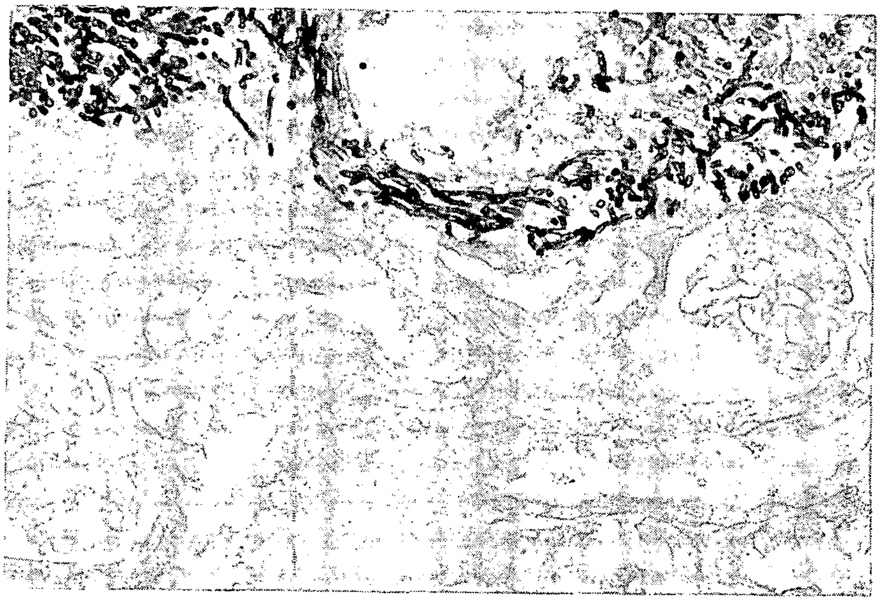

Fig. 2 *Renal biopsy (Grocott's stain 285). Positively-staining filaments of Candida albicans are seen at the edge of the renal cortical tissue. Two glomeruli are seen, one on the lower left-hand side, the other on the right.*

Krill, 1970). Systemic candidiasis is rare in the healthy infant. However, with the increase in intensive care of the newborn systemic candidiasis may become more common. For effective treatment early diagnosis is essential and there may be clues: the growth of *Candida* from a cannula tip, or the appearance in the urine of budding yeast cells and, in particular, hyphae (Bernhardt *et al.*, 1974). Indeed urine examination and cultures may be a more reliable method of diagnosis than venous blood culture (Stone, 1974).

Candida infection of the urine, although rare, may occur at any age. Most urine infections are not accompanied by systemic candidiasis or by renal involvement (Littlewood, 1968). Gherardi (1965) reported a baby who presented with severe hypertension resulting from renal artery fungal obstruction. Acute renal failure has not been considered a complication of either systemic or urinary candidiasis in children, although there are reports of its occurrence in adults (Louria *et al.*, 1962; Lehner, 1964).

We thank Dr John Davies for the information about the infant's early life, and Dr Evans and Dr Mason for technical help. We acknowledge, with gratitude, the sustained efforts of the nursing and medical staff in Grimsby and Leeds; their help so nearly succeeded in saving the baby.

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Leukaemic hypopyon in acute lymphoblastic leukaemia after interruption of treatment

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SUMMARY A 7-year-old girl was successfully treated for acute lymphoblastic leukaemia, and remained in remission after treatment had been completed in 3 years. Four months after cessation of treatment, iridocyclitis with hypopyon developed in one eye. Exudate from the anterior chamber contained numerous lymphoblasts. Local radiotherapy led to complete resolution of the ocular lesions, and the patient remains well 22 months later.

Leukaemic involvement of the retina, optic nerve or, occasionally, of the anterior chamber of the eye, was recorded by Ridgway *et al.* (1976) in 9% of acute lymphoblastic leukaemia (ALL) cases in children, and is often demonstrable at necropsy (Sansone and Mariotti, 1953; Allen and Straatsma, 1961; Evans, 1964; Kearney, 1973; Mark *et al.*, 1974; Ridgway *et al.*, 1976; Murray *et al.*, 1977). We describe hypopyon as an isolated occurrence in a case of ALL 4 months after treatment had been stopped.

Case report

A 7-year-old girl with ALL was treated with vincristine 2 mg/m^2 weekly for 5 weeks, together with prednisone 50 mg/m^2 daily for one month, and full remission was obtained. CNS prophylaxis was then given with 2400 rads of ^{60}CO cranial irradiation in 24 days, and intrathecal methotrexate 6 mg/m^2 weekly for 6 weeks, repeated every 3 months for the next 18 months. Remission was maintained on 6–mercaptopurine (6–MP) 50 mg/m^2 daily and methotrexate 20 mg/m^2 weekly. Reinduction therapy was given every 3 months: vincristine 1·5 mg/m^2 weekly for 3 weeks; prednisone 30 mg/m^2 daily for 3 weeks. After 3 years of complete remission, treatment was stopped in April 1976.

Four months later, while still in complete haematological remission, our patient complained of severe photophobia. The left eye showed perikeratic injection, infiltration and congestion of the iris, and copious whitish hypopyon which occupied almost half of the anterior chamber; there was absence of synechiae, little aqueous flare, and the pupil was round central and reacting. The right eye was normal. The haematological findings remained normal, as did the bone marrow biopsy and the cerebrospinal fluid (CSF). A diagnosis of iridocyclitis was made, and local treatment with atropine and cortisone, with antibiotics and dexamethasone systematically, was begun.

Within 3 weeks there was complete regression of the ocular lesions and treatment was stopped. Two months later the ocular condition recurred in the left eye. The same treatment was repeated, but after 10 days there had been no improvement, and a subconjunctival injection of betamethasone was given. During the next 10 days there was progressive absorption of the hypopyon with some residual swelling of the iris. The eye returned to normal after a further month of local treatment (atropine and cortisone).

Two months later there was a second relapse with similar appearances of the left eye, this time with haemorrhagic striae mixed with the hypopyon. Treatment (atropine, cortisone locally, and subconjunctival injection of betamethasone) resulted only in some relief of symptoms, but shortly afterwards there was copious hypopyon. Fluid was then withdrawn from the anterior chamber of the left eye and this showed a cell population composed mainly of lymphoblasts. Bone marrow and CSF remained normal. A diagnosis of leukaemic hypopyon was made. Radiotherapy (total of 390 rads in a 22-day period) to the anterior segment of the eye was given and resulted in complete remission. Further systemic treatment (vincristine and prednisone, followed by 6–MP and methotrexate) was then given.

After 22 months, the clinical and haematological findings remain normal.

Discussion

Ridgway *et al.* (1976) suggested that the eye, because of its anatomical structure, can behave as a 'pharmacological sanctuary' in leukaemia. The anterior segment is the most rarely affected site within the eye, but a few other cases have been reported (Kearney, 1973; Mark *et al.*, 1974; Murray *et al.*, 1977). In all these reported cases however, this complication occurred during haematological relapse or in association with meningeal leukaemia. In our case the patient was off treatment and there were no other leukaemic manifestations.

Although radiotherapy to the eye proved effective, a case such as this must be regarded as having relapsed and therefore requiring further courses of antileukaemic drugs.

We thank Professor F. Fossati who performed ocular radiotherapy.

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Reye's syndrome associated with respiratory syncytial virus infection

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SUMMARY An upper respiratory tract infection in a 22-month-old boy was followed by rapid loss of consciousness, hypoglycaemia, uraemia, and death. Necropsy examination showed fatty change of liver and kidneys, severe cerebral oedema, bronchiolitis, and endocardial fibroelastosis affecting the left ventricle. Immunofluorescence staining showed infection with respiratory syncytial virus (RSV). The clinical and pathological findings were those of Reye's syndrome, not previously reported accompanying RSV infection.

Reye *et al.* (1963) described a syndrome of acute encephalopathy and fatty degeneration of the viscera. The association with an acute respiratory virus infection has often been noted, but respiratory syncytial virus (RSV) has not, to our knowledge, been implicated. We report a fatal case of Reye's syndrome associated with a RSV infection.

Case report

A boy of 22 months developed a mild upper respiratory tract infection with nonproductive cough and coryza which was treated with a proprietory linctus. On the 3rd morning he did not wake at the usual time but was seen by his mother at 8.30 a.m. to be sleeping peacefully with normal respirations. At 9.30 a.m. she found him blue, limp, and dyspnoeic.

On admission one hour later he was found to have peripheral vasoconstriction, central cyanosis, and to be in shock. Systolic blood pressure was 60 mmHg, pulse 88/min, and respiratory rate 48/min. He responded only to painful stimuli, his respirations were shallow, noisy, and irregular. There was diminished air entry, particularly on the left, coarse moist sounds and expiratory rhonchi were present bilaterally. The liver was not palpable. Retinal examination and reflexes were normal. His condition deteriorated rapidly; coma deepened, muscle tone increased, plantar responses became extensor. Treatment with dextrose/saline, hydrocortisone, antibiotics, and oxygen was ineffective; he died 3 hours after admission.

Investigations. Total WBC count 18 800/mm^3 (18·8 × 10^9/l) with mild neutrophilia, blood urea 69 mg/100 ml (11·5 mmol/l), bicarbonate 17 mEq/l, blood sugar 10 mg/100 ml (0·56 mmol/l), CSF and blood cultures were sterile. Nose and throat swabs yielded normal flora.

Necropsy. A well nourished baby boy 89 cm crown/heel length, weighing 11·6 kg. The brain was swollen (1170 g); slicing after fixation showed obliteration of sulci. The larynx was injected, trachea and main bronchi contained purulent mucus, and the epithelium was swollen and purplish. The lungs were bulky with petechial haemorrhages and foci of collapse throughout (right 110 g, left 102 g). The heart was slightly enlarged (64 g) but anatomically normal, left ventricular hypertrophy and dilatation with pearly white thickening of the left ventricular endocardium was present, valves healthy. The liver was enlarged (554 g), pale yellow, and greasy to touch. Other organs were healthy.

Histological examination of the liver showed gross fatty change throughout the lobules and fat droplets present in renal tubular epithelium. In the lung, bronchi and bronchioles were plugged with mononuclear cells, lining epithelium was cuboidal, and the wall infiltrated by inflammatory cells with patchy extension into alveoli. A subendocardial layer of fibroelastic tissue was present in the left ventricle. There was cerebral oedema but no inflammatory cell infiltration of brain or meninges.

Virological investigation. Secretions aspirated from the nasopharynx, on admission, were inoculated on to tissue cultures on monkey kidney, human amnion, and Hep 2 cells. No virus was isolated. Cells from the aspirate stained by the immunofluorescence technique of McQuillin and Gardner (1968) showed specific fluorescence for RSV.

Brain tissue collected at necropsy was inoculated on to human amnion and monkey kidney cells, but no virus was isolated. Post-mortem lung also failed to yield virus when cultured on the same cells as the aspirate. A piece of lung, 10 × 10 × 5 mm, was snap frozen and sections, 6 μm thick, were cut in a cryostat, air-dried, and fixed with acetone. Sections were stained for RSV using bovine antiviral serum* (1:80) and fluorescein conjugated rabbit antibovine globulin* (1:40). Control sections were treated with bovine serum free of antibody. In each test section there were 2 or 3 small bronchi with fluorescent cells in the epithelium (Figure); no such fluorescence appeared in the control sections.

Complement-fixation tests on serum collected at necropsy gave the following titres: parainfluenza virus 1:16; mumps 1:8; RSV influenza A, *Mycoplasma pneumoniae*, psittacosis, *Coxiella burnetii*, herpes simplex virus, and cytomegalovirus all 1:8.

Discussion

The aetiology of Reye's syndrome is still uncertain. An association between it and various drugs and chemicals has been reported (Glasgow and Ferris, 1968; Shield *et al.*, 1977) but there does not seem to be an association with a particular molecular configuration. The frequency of a mild prodromal illness may partly explain the association with salicylate ingestion, although in one report several children were taking high doses of salicylate (Linneman *et al.*, 1975). Aflatoxin ingestion has been incriminated in some countries, but its precise role is unknown (Hogan *et al.*, 1978). The most commonly reported association is that of Reye's syndrome and virus infection. Influenza B virus is the most often implicated although in some cases infection with influenza A, parainfluenza, and adenovirus or varicellazoster virus has been shown by isolation or serology (Linneman *et al.*, 1975). In this case, RSV was demonstrated by immunofluorescence but was not isolated in tissue culture, which is not unexpected as this virus is difficult to grow from necropsy specimens. The histological appearances of the lungs in this child are typical of bronchiolitis. The presence of endocardial fibroelastosis may have contributed to this boy's death; some children with this condition die suddenly and unexpectedly, but many more are precipitated into heart failure by an apparently trivial infection. Heart failure alone would not be expected to produce severe panlobular fatty change in the liver but rather a centrilobular distribution of fatty change, possibly associated with necrosis. Similarly, renal tubular fatty change could not be attributed to heart failure.

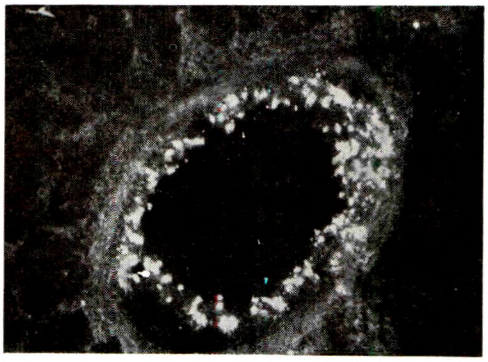

Figure *Immunofluorescence staining of RSV antigen in the epithelial cells of a small bronchus.* (× *180*).

Reye's syndrome has not been reported previously as a complication of RSV infection and it is perhaps of particular interest that a bronchiolitis rather than a pneumonia is present in this case, in view of the suggestion that bronchiolitis is an allergic response to a virus antigen (Gardner *et al.*, 1970). The association of Reye's syndrome with a variety of virus infections and the absence of viral invasion of brain or liver suggests the participation of an additional factor, metabolic or toxic, in the pathogenesis of this condition.

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*Wellcome Reagents Ltd.

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Chloramphenicol and phenobarbitone—a drug interaction

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SUMMARY Two infants with meningitis who were treated with phenobarbitone and high-dose chloramphenicol showed progressive falls in the peak blood levels of chloramphenicol. A standard chloramphenicol dose of 50 mg/kg daily would have produced subtherapeutic blood levels after only a few days. The importance of measuring serial blood chloramphenicol concentrations is stressed.

Infants and young children with bacterial meningitis are often treated with phenobarbitone to prevent convulsions. Chloramphenicol is the antibiotic of choice for the treatment of *Haemophilus influenzae* meningitis. A possible interaction between these two drugs is recognised (Bella *et al.*, 1968) but has not been specifically reported in man. We therefore report two infants with *H. influenzae* meningitis treated with phenobarbitone and chloramphenicol, in whom peak blood levels of chloramphenicol decreased with time in spite of maximum recommended dosage. The first case alerted us to the problem, the second prompted a more detailed study.

Case reports

Case 1. This 7-month-old girl presented with a 4-day history of upper respiratory infection, followed on the day of admission by fever, lethargy, irritability, and refusal to feed. Cultures of blood and CSF gave a pure growth of *H. influenzae*, sensitive to chloramphenicol. She was treated with IV chloramphenicol succinate (100 mg/kg per 24 h) plus phenobarbitone (10 mg/kg per 24 h). Blood chloramphenicol concentration was measured by bioassay based on the method described by Louie *et al.* (1976). Peak blood chloramphenicol levels were 31 mg/l on days 2 and 3 but they fell to less than 5 mg/l on day 5. On day 6 oral treatment with pure chloramphenicol in the same dose was substituted. On day 8 the peak blood level was still <5 mg/l and the dose of chloramphenicol was therefore doubled (200 mg/kg per 24 h). Subsequently, peak blood levels of between 7 and 11 mg/l were maintained until day 23, when treatment was stopped. Her subsequent progress was unremarkable and she remains in good health 12 months later.

Case 2. This 3-month-old boy presented with a one-day history of vomiting, fever, lethargy, and irritability culminating in a brief convulsion. Cultures of blood and CSF gave a pure growth of *H. influenzae*, sensitive to chloramphenicol. He was treated with IV chloramphenicol succinate (100 mg/kg per 24 h) for 8 days, before being changed to oral pure chloramphenicol in the same dosage. He was treated throughout his illness with phenobarbitone (10 mg/kg per 24 h). Chloramphenicol was given for a total of 19 days and he made a full recovery. Although chloramphenicol blood levels were initially satisfactory, they fell rapidly during the first few days of IV treatment (Figure). The biological half-life of chloramphenicol fell from 7 h 18 min on the 3rd day to 4 h 6 min on the 5th.

Discussion

90% of chloramphenicol is inactivated in the liver either by conjugation with glucuronic acid or by reduction to aryl amines before being excreted in the urine. The remaining 10% is excreted unaltered in the urine. In these two infants there was a rapid

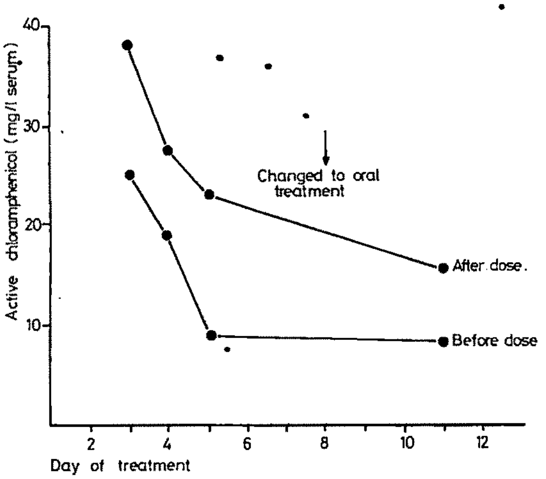

Figure (*Case 2*) *Blood levels of active chloramphenicol during treatment with chloramphenicol 100 mg/kg per 24 h plus phenobarbitone 10 mg/kg per 24 h. Blood levels were measured before and one hour after the 12 midday dose.*

decline in chloramphenicol blood levels despite sustained IV treatment in high dosage. This decrease is probably explained by the induction of hepatic microsomal enzymes by phenobarbitone. Increased glucuronidation of chloramphenicol and a consequent decrease in therapeutic activity have been demonstrated in rats pretreated with phenobarbitone (Bella *et al.*, 1968).

The conventional chloramphenicol dose for meningitis and septicaemia is 50–100 mg/kg per 24 h in infants and children. A lower dose is usually recommended for neonates whose renal and liver immaturity delays chloramphenicol excretion, but Black *et al.* (1978) showed that doses of up to 95 mg/kg per 24 h may be needed to maintain therapeutic blood levels in this age group also. Our two patients show that during treatment with phenobarbitone even the maximum recommended dose of chloramphenicol, 100 mg/kg per 24 h, may be insufficient to maintain peak blood levels within the therapeutic range 15–25 mg/l. We therefore recommend that in all patients who receive enzyme-inducing anticonvulsants (Conney, 1967), chloramphenicol blood levels should be measured every one or 2 days to avoid the hazards of excessive or inadequate dosage. It is possible that newer anticonvulsants with less enzyme-inducing activity, such as sodium valproate, will prove to have less effect on chloramphenicol metabolism than phenobarbitone.

We thank Mrs Barbara Tennant for secretarial help.

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Food allergy

Response to treatment with sodium cromoglycate

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SUMMARY Two children with food allergy could not be successfully managed on dietary restriction alone. There was a good response to treatment with oral sodium cromoglycate but none to placebo treatment. The use of sodium cromoglycate in the management of food allergy should be studied further.

Allergy to cows' milk and other foodstuffs presents a difficult problem in diagnosis and management in children. Diagnostic criteria were discussed by Walker-Smith (1975). Reports by Freier and Berger (1973) and Kuzemko and Simpson (1975) suggested that treatment with oral sodium cromoglycate might relieve symptoms. Two children are reported who demonstrated specific food intolerance, and their response to treatment with oral sodium cromoglycate is described.

Case reports

Case 1. A baby girl was breast fed for the 1st month of life and subsequently was given a dried milk (Ostermilk). After the change to artificial feeding her weight gain was unsatisfactory and she had persistent respiratory symptoms. When the patient was one-year old, her mother concluded that the child was allergic to milk and discontinued milk feeds. There was an almost immediate cessation of symptoms and her rate of weight gain returned to normal. She returned to milk-containing products in her diet at age 2 years. After this she developed eczema which did not respond well to local treatment. She had recurrent episodes of abdominal pain and loose stools. Attempts to eliminate milk from her diet were unsuccessful as she had access to milk products in neighbours' houses and from other children. Eczema, abdominal pain, and diarrhoea were her most significant symptoms and their severity was related to ingestion of milk products or milk. Immunoglobulin studies showed a slightly raised serum IgE of 240 IU/ml (normal 20–120 IU/ml) at age 4½ years. C3, C4, and C1 INH were normal.

Treatment with oral sodium cromoglycate 100 mg four times daily was begun at age 4½. After one year there was a significant improvement in her overall state of health. The eczema had disappeared; her previously dry and ichthyotic skin became normal. Her diet at this time included milk-containing products—butter, bread, coffee, cakes, milk chocolate—and these were well tolerated without adverse reaction. Her weight had increased from the 3rd to the 10th centile. After one year it was decided to test her dependence on the treatment in the hope that it could be discontinued. Therefore, alternate episodes of treatment with sodium cromoglycate capsules and placebo capsules were given. During the period of placebo treatment, her eczema and gastrointestinal symptoms returned and she became a miserable, irritable child. During treatment with sodium cromoglycate she remained well. It was therefore decided that she should continue with the sodium cromoglycate orally indefinitely.

Case 2. A boy had severe eczema from age 2 years. He developed asthma at 7 and at about this age had a severe urticarial rash on several occasions. The rash was related to the ingestion of certain foodstuffs: pork, bacon, tomato soup, sage and onion stuffing, fish. Serum immunoglobulin and complement studies were normal. In view of the history he was given 100 mg sodium cromoglycate orally before ingestion of a known allergen (sage and onion stuffing) and he developed a mild urticarial reaction. He was subsequently given 200 mg oral sodium cromoglycate and after ingesting the same allergen he had no reaction. He was next treated for one week with sodium cromoglycate 200 mg orally, four times daily. Then, after a week of no treatment he was treated with placebo. During the period of treatment with sodium cromoglycate he had no episodes of urticaria, but while taking the placebo these occurred severely each day (Table). He has since remained on sodium cromoglycate 200 mg orally, four times daily. His eczema has resolved and he has no episodes of urticaria, except when he forgets his treatment. On starting the sodium cromoglycate he had transient mild swelling of his face which settled in a few days.

Table (*Case 2*) *Response to treatment with sodium cromoglycate* (*oral*)

Sodium cromoglycate (oral)	*Allergens*	*Response*
None	Sage and onion stuffing	Severe urticaria
100 mg	,, ,, ,,	Mild urticaria
200 mg	,, ,, ,,	None
200 mg 4 times daily × 1/52	Bacon	Mild
	Tomato soup	Mild
Placebo × 1/52	Fish Bacon Pork	Brisk reactions each day

Discussion

The range of symptoms which can occur as a result of exposure to food allergens include anaphylactic shock, asthma, rhinitis, urticaria, eczema, and gastrointestinal disturbances (Blanckaert *et al.*, 1975). The clinical diagnosis was established by the absence of symptoms after dietary elimination of the allergen, and recurrence of symptoms after reintroduction of the allergen. Elimination of specific allergens from the diets of young children is difficult to achieve as the child will accept food given to him by other children, neighbours, and friends unaware of the restrictions. Oral sodium cromoglycate offers a possibility of protection from food allergens as its mechanism of action lies in the inhibition of degranulation of mast cells, preventing the release of histamine and slow reacting substance A (Werthenschlag, 1975). It has been reported (Moss *et al.*, 1971) that less than 2% of orally-administered sodium cromoglycate is absorbed. It is probable that allergic symptoms are prevented by the unabsorbed portion of the drug passing through the gut. No large-scale study has been reported on the use of oral sodium cromoglycate in the management of cows' milk or other food allergy, but these observations demonstrate its usefulness in specific cases.

We thank Professor R. D. G. Milner for help and permission to present these cases, Fisons Ltd for supplies of oral sodium cromoglycate, and Drs A. Milford Ward and J. Watkins of the Department of Immunology, Hallamshire Hospital, Sheffield.

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Archives of Disease in Childhood, 1979, **54**, 80–83

Correspondence

Renin and aldosterone response in human newborns to acute blood volume change

Sir,

We read with interest the report of Dillon and associates (*Archives*, 1978, **53**, 461) on this subject. In a paper to be submitted to *Rivista Italiana Pediatria* we studied plasma renin activity (PRA) in 13 newborn infants undergoing exchange transfusion with ACD stored blood for hyperbilirubinaemia of various aetiology during the first 6 days of life. Exchange transfusions were such that the infants were kept normovolaemic. Weights ranged from 2400 to 3810 g, and gestational ages from 37 to 41 weeks. PRA and haematocrit were determined on umbilical vein samples before, midway, and at the end of the procedure, and from the transfused blood. The amount of blood administered ranged from 63.7 to 155.8 ml/kg, and the exchange rate from 0.964 to 5.288 ml/kg per min.

Statistical analysis of data was performed by a step-wise multiple regression program (UNIVAC 90/30), taking into account as dependent variable the average rate of renin production during the period of exchange transfusion and as independent variables the weight, postnatal age, basal PRA of the newborn, donor's PRA, and exchange rate. Allowing for the dilution caused by the donor's blood, hyperproduction of renin occurred in all cases. All these variables influenced, in various directions, the rate of renin release but the rate of exchange appears to be the most important factor in the activation of the renin-angiotensin system (multiple correlation coefficient = 0.774; F-value for analysis of variance = 16.404; standard error of estimate = 0.078; t = 4.050; $P < 0.01$).

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Familial neurodegenerative disorder associated with raised urinary VMA

Sir,

The belief held by Young and Hosking (*Archives*, 1978, **53**, 682) that 'disturbances of catecholamine excretion have not been known to occur in children with a progressive neurological disorder or other neurological insult' is not true. Excessive urinary excretion of 4-hydroxy-3-methoxymandelic acid (HMMA) has been demonstrated in hydrocephalic infants with spina bifida (Barson and Hodge, 1971). It was felt from this study that a raised urinary HMMA reflected a persistently raised intracranial pressure, since it was not a feature of spina bifida alone or in cases where hydrocephalus was well controlled by a valve. It is likely that increased excretion of catecholamines is a nonspecific consequence of degenerating nerve tissue, whether this is in turn due to increased intracranial pressure or to an intrinsic neurological disorder.

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Dr Hosking comments:

We are grateful to Dr Barson for drawing our attention to his important paper. It was remiss of us not to be aware of the data in that publication.

The raised levels of urinary HMMA seen in Drs Barson and Hodge's papers are most likely nonspecific as Dr Barson suggests. Similar increases are seen from time to time in a number of 'stress' situations. However, in our patient there was not only biochemical evidence of impaired catecholamine metabolism or excretion, but also clinical features apparently related directly to this abnormality. It is for this reason we suspect our patient's disordered metabolism was rather more specific.

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Peripheral pulmonary artery stenosis

Sir,

The observation by Salisbury and Keeling (*Archives*, 1978, **53**, 428) of polypoid lesions in the peripheral pulmonary arteries of an infant, recalls a controversy that was resolved over 20 years ago. Originally described in systemic arteries by Bucciante in 1945 and later by many others, these structures became known as 'pedunculated nodules' or 'polypoid cushions' and were interpreted as flow regulation mechanisms. Later studies

(Wagenvoort and Planten, 1954; Staubesand, 1955) produced morphological evidence that they were artefacts and that they resulted from invaginations of the arterial wall when tissues are stretched and then cut. This may happen during surgery as well as at necropsy. Moffat (1956) produced these changes, which are identical with those described by Salisbury and Keeling, experimentally.

As for the pulmonary vasculature, in our experience they are found particularly often in the thick-walled pulmonary arteries of newborn infants and of patients with pulmonary hypertension of whatever cause (Wagenvoort *et al.*, 1964), while in normal adult individuals they are usually limited to the elastic pulmonary arteries and do not occur in the thin-walled muscular arteries in which the tendency to invaginate is apparently much less.

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Dr Keeling comments:

We are aware that vascular 'abnormalities' may be produced by the casual treatment of tissues. The lungs in this case were fixed before blocks were taken for histological examination and we note that Moffat (1956) was unable to produce vascular 'lesions' when tissues were treated in this way; nor were we, on re-examination of semiserial sections of the lungs, able to find evidence of local vessel damage, thus excluding reported causes of artefact.

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Moffat, D. B. (1956). On the so-called 'polypoid' cushions in arteries. *Acta anatomica*, **26**, 110–120.

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Weaning very low birthweight infants from mechanical ventilation using intermittent mandatory ventilation and theophylline

Sir,

We would like to support the observations of Dr Barr (*Archives*, 1978, **53**, 598) who found that theophylline therapy facilitated the weaning of infants from mechanical ventilation when apnoea and bradycardia occurred at low IMV rates. We have used this combination therapy in 2 infants with hyaline membrane disease (1620 g, 32 weeks' gestation; 2000 g, 34 weeks' gestation). Theophylline serum concentrations were closely monitored, and all were in the therapeutic range (6 to 11 mg/l). Both infants were severely ill. Each had bilateral pneumothoraces requiring chest tube drainage. Both developed significant apnoea and bradycardia at IMV rates less than 5, necessitating increased ventilatory support primarily in the form of repeated bagging during apnoeic episodes. The infants had dramatic responses to treatment with theophylline, and we were able to extubate both infants within 48 hours.

We too believe that theophylline can aid in weaning infants from ventilators when apnoea and bradycardia occur at low IMV rates. Theophylline can be beneficial not only for low birthweight infants but also for those in whom rapid extubation or a reduction in mean intrathoracic pressure is desirable. Our infants with pneumothoraces are good examples, and others (such as those with pneumopericardium) come readily to mind.

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Detection of phenylketonuria

Sir,

Guthrie testing is performed at this hospital on blood samples received from the whole of Scotland, from children aged 6 to 14 days (Stevenson and Kennedy, 1974). Samples are assayed for phenylalanine, tyrosine, methionine, leucine, and galactose, blood samples being collected by hospitals or health visitors as appropriate, and a check on samples received compared with the number of registered births by the district medical officer.

Theoretically, therefore, all children should be included in this national scheme; although in practice the percentage of children sampled varies from 93–99% (Clayton, 1976).

In a recent search for the PKU cards of children born in Glasgow of known birth dates for another purpose, a surprising number of samples had either never been received by the hospital, or had not been taken within the recommended time of 6 to 14 days. Of 1000 sequential samples received from the Glasgow area during 4 weeks in 1977, in 4.2% of cases the child was 6 days old when the specimen was assayed, and must therefore have been less than 6 days old when the sample was taken. 93.8% of samples were taken at an 'acceptable' age of 7 to 21 days old; but in the remaining 2% of cases, the child was over 3 weeks old before the test was done; in 0.8% of cases, representing 100 samples per year in Glasgow, or 700 in Scotland, the child was more than 2 months—in some cases, as much as 7 months old.

Obviously in these cases the value of the test is much reduced, with the possibility that permanent brain damage would already have occurred before it was performed. This has two consequences—firstly, doctors who are working with sick young children should be aware that they may not have had inborn metabolic errors excluded by the National Screening Programme; secondly, if neonatal screening is to be extended to other conditions of personal or economic importance, such as hypothyroidism or lead poisoning, a truly fail-safe and universal screening programme would be needed, if it is to justify its cost.

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Early onset of homozygous β^{0} thalassaemia associated with neonatal jaundice

Sir,

I read with interest the paper by Furbetta *et al.* on this subject (*Archives*, 1978, **53**, 250). Although they stated that 'all other common causes of neonatal jaundice had been excluded', the ABO set-up (blood group of baby A and the mother O) which is the most common cause of jaundice in the newborn, was present. In ABO incompatibility, the direct Coombs's test is usually negative. Therefore this possibility should be ruled out before ascribing the neonatal jaundice to thalassaemia.

I should also like to add that among our 90 patients with thalassaemia major (until 1970) pallor and distended abdomen were noticed at birth in two, at 17 days of age in one, at 20 days in one, at 30 days in two, and at about 40 days in two; the observation of splenomegaly as early as 17 days of age in one, might indicate that Cooley's anaemia in this area becomes symptomatic very early as stressed by the authors.

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Professor Cao comments:

The letter from Prof. S. Ozsoylu raises the possibility that the neonatal jaundice could have been due to ABO incompatibility.

However there was evidence of a moderate haemolytic process with Hb level of 13 g/dl in the 5th day, and the jaundice was first noted on the 3rd day, while in ABO incompatibility there is usually little or no evidence of a haemolytic process, and hyperbilirubinaemia appears usually within 24 hours of birth. Moreover, microspherocytosis, a prominent feature of ABO haemolytic disease, was absent.

The direct Coombs's test on the infant's erythrocytes was negative, while in our laboratory, as in others, a weakly positive reaction in ABO haemolytic disease is common. Finally when there is ABO incompatibility it is our custom to test the eluate from the erythrocytes of the affected newborn with A (or B) adult cell. This reaction was negative, and not strongly positive as found usually in ABO haemolytic disease. ABO haemolytic disease cannot be ruled out with certainty in this case but the evidence makes this diagnosis highly improbable.

Prof. Ozsoylu comments that in the population under his care Cooley's anaemia often presented early. In the last year we diagnosed 80 new cases of Cooley's anaemia due to homozygous β^{0}-thalassaemia. An early presentation with criteria such as symptomatic anaemia (Hb <7–8 g/dl) at 75-90 days was observed in 30% of cases, but the severe anaemia (Hb <6 g/dl) at 60 days as seen in our patient was rather uncommon. Splenomegaly in cases with earlier presentation is an unusual feature in this area. The age and clinical findings at presentation in Cooley's anaemia varies in different ethnic groups. This may be due to the genetic heterogeneity of the disease and different environmental conditions.

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Successful restoration of immunity in the DiGeorge syndrome with fetal thymic epithelial transplant

Sir,

I read with interest the paper by Thong *et al.* on this subject (*Archives*, 1978, **53**, 580). The authors stated that correction of the hypocalcaemia was achieved by the use of

AT10 (vitamin D2); in which AT10 was considered as equivalent to vitamin D2. AT10 (dihydrotachysterol) is quite different from vitamin D2 which is ergocalciferol. Although both compounds, after their hydroxylation in the liver and kidney would be effective on serum calcium levels, they differ in that AT10 may be rachitogenic in long usage but vitamin D is the compound recommended for the prevention and treatment of rickets.

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Drs Thong and Robertson comment:

We thank Professor Ozsoylu for his correction of our error. AT10 (dihydrotachysterol) is a reduction product of vitamin D and differs from vitamin D in the geometrical configuration of the A ring. This product has been used in the treatment of hypoparathyroidism for many years, and is preferred to calciferol by some because of its more rapid onset of biological activity and its more rapid excretion (Root and Harrison, 1976). We have seen no evidence of a rachitogenic effects in patients with hypoparathyroidism treated with either dihydrotachysterol or calciferol, nor have we seen such a report in the literature.

Perhaps Professor Ozsoylu's concern is based on the *in vitro* work of Trummel *et al.* (1971) and Reynolds *et al.* (1973) who showed a direct effect of both dihydrotachysterol and its 25-hydroxylated metabolite, 25-hydroxy-dihydrotachysterol on bone resorption in culture, which was greater than the effect of 25 hydroxycholecalciferol.

Both calciferol and dihydrotachysterol have been used effectively in the long-term management of hypoparathyroidism. Since, in the absence of parathyroid hormone, the production of the most active form of vitamin D, 1, 25-hyhidroxycholecalciferol is impaired, a more rational form of therapy would be this product or its synthetic analogue, 1α-hydroxycholecalciferol which have been shown to be effective. These products are not yet generally available (Russell *et al.*, 1974).

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Archives of Disease in Childhood, 1979, **54**, 84

Book review

Pediatric Urologic Surgery. Edited by H. B. Eckstein, R. Hohenfellner, and D. I. Williams. (Pp. 533; illustrated + tables. £66.25 hardback.) Holt-Saunders: Eastbourne.

This surely is one of the finest operative texts yet produced and it will remain for some decades the most comprehensive and authoritative guide for all those tempted to operate on the urological problems of children. The timing of the production of this beautifully produced book is excellent as it coincides appropriately with the retirement from active paediatric urological practice of the senior author, Innes Williams, who has done more than anyone for this subject. Furthermore, it is only in the last year or two that techniques of this rapidly expanding specialty have become standardised although where there are still considerable controversies, as, for example with hypospadias, the book provides good coverage of many different techniques. Many operations such as penile lengthening and paediatric transplantation are not easily found elsewhere. Although the more complicated procedures in paediatric urology should not be performed by those who have not had adequate training in both urology and paediatric surgery, here at least is advice on how to perform safely virtually all operations one is likely to encounter.

The illustrations must be singled out for their excellence and it is pleasing to see the radiologists and anaesthetists writing as part of the team. Here is a book by internationally renowned experts that although expensive, as are all such good books, will be a prize possession for all those interested in this subject.

R. WHITTAKER

Shorter notice

Major Mental Handicap: Methods an Costs of Prevention. Ciba Foundatio Symposium 59 (new series). (Pp. 226 illustrated + tables. US $23.00 hardback Excerpta Medica: Amsterdam.

A Ciba symposium held in London i November 1977 with contributions from USA, Canada, France, Sweden W. Germany, Switzerland, Finlan besides the UK. The recent strikin improvement in the infant mortality i France, thought to be a consequence o the active measures initiated by th government, provided no doubt a mai impetus for the idea of 'cost-effectivenes being applied to perinatal work. Th final chapter by Chapalain of Par describing French experiences evaluating cost-benefit is thus particular worth while.

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1. Practical Therapeutics (1975) 10, 112.
2. Postgraduate Medical Journal (1975) 51, 615.

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Hypothalamic and Pituitary Hormones

The Proceedings of a Symposium organised by the Association of Clinical Pathologists

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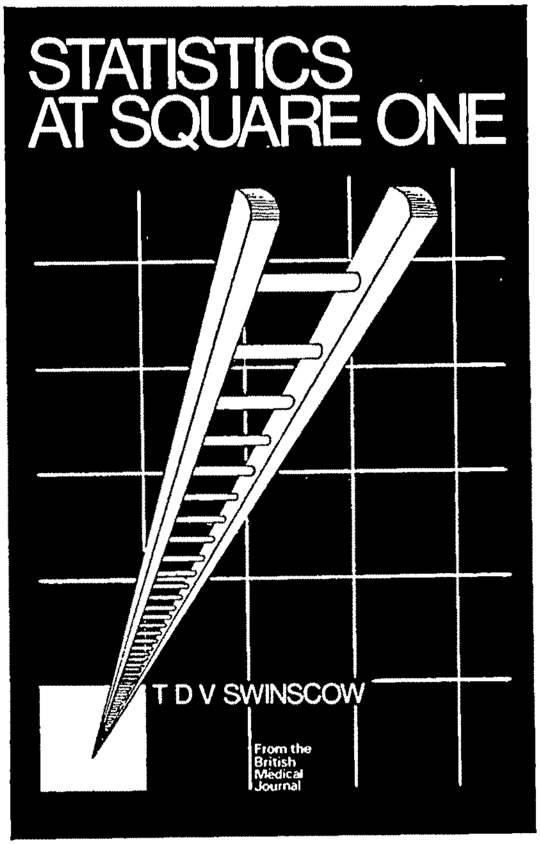
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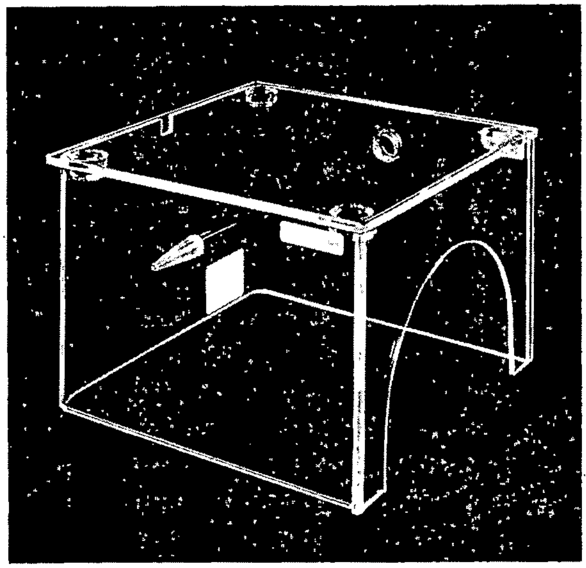

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Archives of Disease in Childhood, 1979, **54**, 85–91

Striatal degeneration in childhood

MAGDA ERDOHAZI AND P. MARSHALL

The Hospital for Sick Children, London

SUMMARY The clinical features, and the radiological and neuropathological findings of 3 unrelated children with striatal degeneration are presented. In one case the father had recently developed choreiform movements while in the other two the family history was negative for neurological disorders. Two patients had juvenile onset of psychiatric symptoms, seizures, and rigidity. The 3rd child presented with focal seizures at 9 weeks of age. The neuropathological findings are virtually identical in all 3 cases. The classification of striatal degeneration in childhood is discussed.

Isolated degeneration of the striate body in childhood is rare and constitutes a diagnostic problem. Patients with juvenile Huntington's disease demonstrate striatal degeneration but the lesion is not usually restricted to that structure. Cases with striatal necrosis have also been described. Three unrelated children with progressive degeneration of the striate body are reported.

Case reports

Case 1. This girl was the first child of unrelated healthy white parents. She was born at term after a normal pregnancy, labour, and delivery and weighed 3·02 kg at birth. There was no family history of neurological disorder, but the father had been adopted and details of his family's medical history are not known. The father remained in good health until about one year after his daughter's death when, at 30 years, he gradually developed choreiform movements. The patient's younger sister, now aged 11, remains in good health. Up to age 5 years, the only abnormalities noted in the patient were a mild dysarthria and a tendency to walk on her toes. At age 5 years she was seen by a psychiatrist because of occasional incontinence and the development of disturbed behaviour characterised by sudden outbursts of crying without obvious reason. Physical examination at that time showed left internal strabismus, slight increase in muscle tone in all extremities, and mild incoordination. Her full scale IQ by the Stanford-Binet test was 92. At age 7½ years she had her first generalised convulsion but no more occurred until a year later. Meanwhile, a slow deterioration in her mental capacity became evident and at age 8 years her IQ had dropped to 54.

She was first seen at The Hospital for Sick Children at age 9 years. During the previous year she had had increasingly severe generalised, akinetic, and myoclonic seizures which responded poorly to a variety of anticonvulsant medications. On examination she was alert, co-operative, but obviously mentally retarded. Her head circumference (49 cm) and her height were at the 3rd centile. She had an impassive facies and mild ptosis of the left eyelid. There was difficulty in initiating movements and postural control was poor. She had a fine resting tremor and an unsteady tip-toe gait. Generalised rigidity was noted and the tendon jerks were brisk. The plantar responses were flexor.

An electroencephalogram demonstrated multifocal spike discharges, particularly on the left. Electroretinography and visual evoked responses were normal. Nerve conduction studies were normal. Although an electromyogram was suggestive of myopathy, a muscle biopsy was within normal limits. Computerised tomography of the head demonstrated enlargement of the lateral ventricles, particularly anteriorly (Fig. 1). Routine investigations of blood and urine were normal as were serum electrolytes and liver function studies. Serum copper and caeruloplasmin levels were normal. There was no increase in blood pyruvate or lactate. Assays for white blood cell β-galactosidase, arylsulphatase A, and hexosaminidase A and B activity were within the normal range. CSF examination showed no abnormality.

After discharge from hospital, our patient's seizures were better controlled but the tremor and rigidity were increasing. She was admitted to the local

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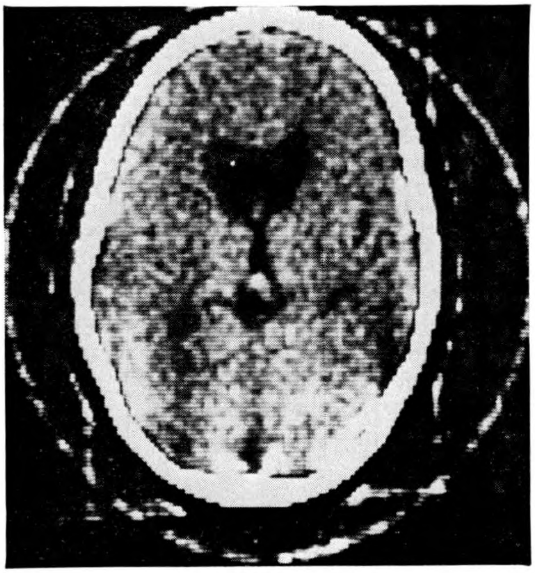

Fig. 1 *Computerised tomogram of the head, demonstrating lateral ventricular enlargement particularly anteriorly in the area of the head of the caudate nucleus.*

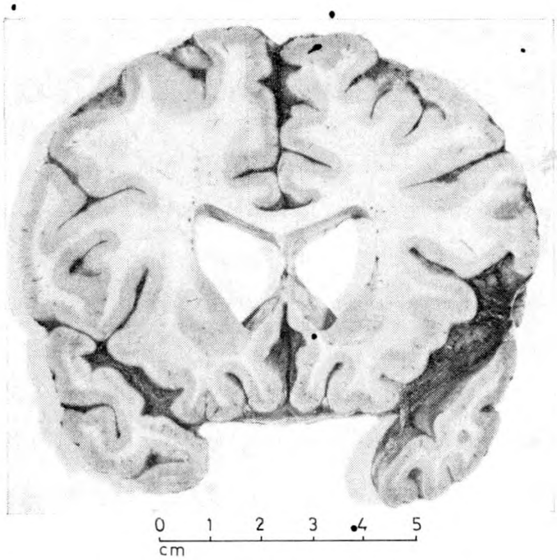

Fig. 2 *Coronal slice of the brain. Note marked shrinkage of the striate body and large lateral ventricles.*

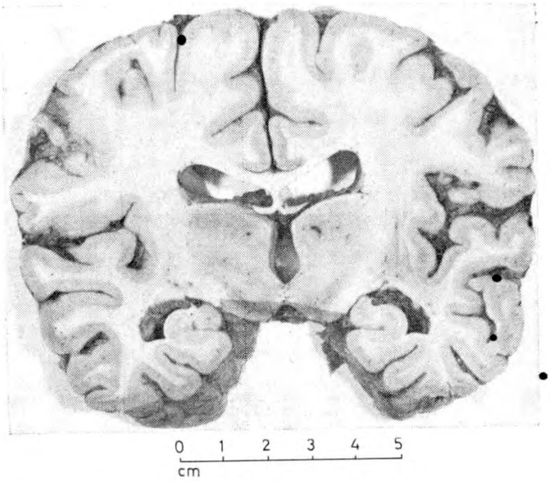

Fig. 3 *Coronal slice of the brain at level of midthalamus. Note marked shrinkage of caudate nucleus and slight shrinkage of thalamus.*

hospital at age 9½ years because she had become too difficult to manage at home. She died 3 months later after further neurological deterioration.

Necropsy (*Dr R. Salm*)
The body was rather thin. No lesions were found except in the CNS.

The brain was reduced in size, the total weight being 1070 g; the cerebellum and brain stem accounted for 154 g. (The average weight of normal brain is 1290 g for this age.) No morphological abnormality was noted externally but coronal sectioning showed enlargement of the lateral ventricles which was more pronounced anteriorly at the level of the striate body. The caudate nucleus and the putamen were shrunken on both sides (Fig. 2). The shrinkage of the caudate nucleus was severe along its entire length, while that of the putamen appeared less marked more posteriorly. There was slight shrinkage of the thalamus and the third ventricle was enlarged (Fig. 3).

Both the caudate nucleus and the putamen showed great loss of neurons, the small neurons being mainly affected. The lesion was increasingly severe caudally. The loss of neurons was accompanied by moderate astrocytic proliferation (Fig. 4). The glial fibre formation was sparse (Fig. 5). Sudanophil or PAS-positive material was not demonstrated in the caudate nucleus or putamen. In sections stained for myelin and axons it was obvious that there was marked loss of the caudato-putaminal and putamino-pallidal fibres (Fig. 6). The globus pallidus and the thalamus showed no neuronal loss or gliosis but the myelin sheaths were weakly staining and there was some loss of axons. Patchy loss of nerve fibres accompanied by demyelination was also present in

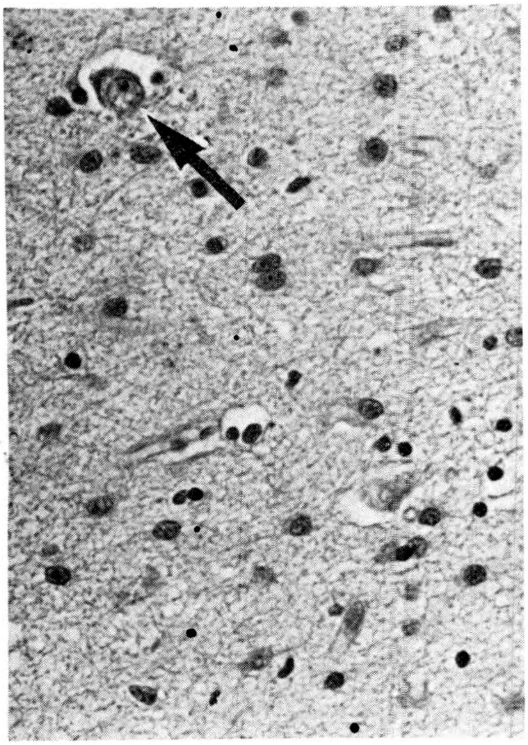

Fig. 4 *Microphotograph of putamen showing a single neuron (arrow) in a field of proliferating astrocytes. H & E ×400.*

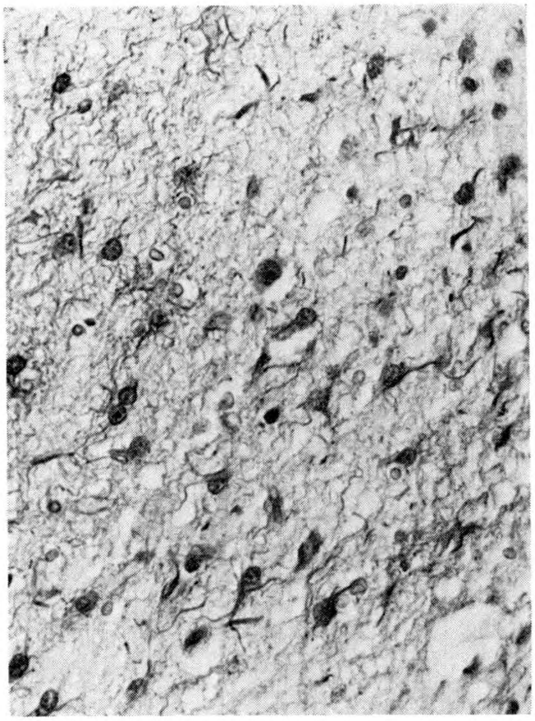

Fig. 5 *Microphotograph of putamen showing astrocytic nuclei with spare glial fibre formation. Holzer ×400.*

the internal capsule. The claustrum, substantia nigra, subthalmic nucleus, red nucleus, and amygdaloid nucleus were intact.

The cerebral cortex showed good preservation in all regions except in the Ammon's horn where there was some neuronal loss and gliosis in the Sommer's sector and endplate. The centrum semiovale and corpus callosum were normally myelinated. The only changes in the brain stem were in the inferior olives. The spinal cord was not available for examination.

The cerebellar cortex showed severe diffuse loss of Purkinje and granule cells with prominent gliosis in all parts. Patchy neuronal loss was observed in the dentate nucleus and the white matter was somewhat pale on myelin staining. The inferior olives showed slight loss of neurons.

Case 2. This baby girl was the 2nd child of non-consanguineous white parents. There is an elder sister, one year older, who remains well. The father died at age 28 years of carcinoma of the stomach. There is no family history of degenerative neurological disease. The patient weighed 3·6 kg at birth and was 2 weeks postmature. Pregnancy, labour, and delivery were otherwise normal. Growth and developmental milestones were normal until 3½ years when she was noted to have a fine tremor of the hands. During the next 2 years she developed increasing clumsiness of gait and slurring of speech. At age 5½ years behavioural problems became evident. She had violent swings of mood with screaming at night and outbursts of violence towards her sister followed by withdrawal and apathy. She was admitted to The Hospital for Sick Children for evaluation.

On examination she was distractible and generally behaved in an immature manner. Her head circumference approximated the 50th centile (50 cm). She had a fine action tremor and was clumsy in manipulating small objects. Her gait was clumsy and awkward. The deep tendon reflexes were brisk. The plantar responses were extensor. Her verbal IQ score was 85 and her performance IQ score was 70 on the Wechsler scale. The neurological examination was otherwise normal. An electroencephalogram demonstrated multifocal spike discharges with variable localisation. During the next year she

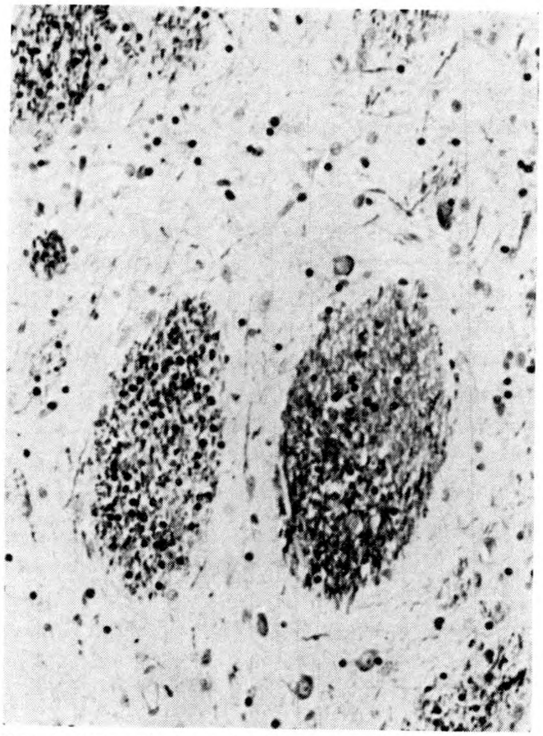

Fig. 6 *Microphotograph of putamino-pallidal bundles showing partial demyelination. Luxol fast blue and cresyl violet. ×240.*

continued to deteriorate. She began to have brief drop attacks and her educational progress ceased. By 6½ years she had developed cogwheel rigidity of all extremities. She was readmitted to hospital. Her head circumference was 52 cm. An air encephalogram was normal. Examination of the CSF showed no abnormality. Blood and urinary amino-acid pattern was normal. Serum copper and copper oxidase levels were normal. At this time she had her first generalised convulsion. Thereafter she had frequent seizures which were generalised, akinetic, or myoclonic in type. Anticonvulsants only partially controlled the convulsions and a course of ACTH did not result in clinical improvement. A trial of benzhexol (Artane) did not alter the rigidity. During the next 18 months repeated admissions were necessary to control her seizures. When admitted at 8 years, she was severely demented and could say only a few intelligible words. She seemed to suffer from terrifying hallucinations and declared she saw insects in her bedclothes and hair. Her head circumference was 51 cm. She was rigid and lay in a 'catatonic' posture with a face lacking any expression. Any voluntary movement of the upper extremities was hampered by severe action tremor. She had difficulty in swallowing which necessitated feeding through a nasogastric tube. All reflexes were brisk. Sustained ankle clonus was present. The plantar responses were extensor. The fundi were normal and there was no abnormality of eye movements. She died of bronchopneumonia at age 8¼ years.

Necropsy

The body was thin with slight flexion contractures of the elbows and knees. The lungs showed bronchopneumonia. No other abnormalities were found except in the CNS.

The brain was reduced in size, the total weight being 1120 g; the cerebellum and brain stem accounted for 133 g. (The average normal brain weight for this age is 1273 g.) No morphological abnormality was noted externally but coronal sectioning showed enlarged lateral ventricles. The enlargement was more pronounced anteriorly owing to the shrinkage of the striate bodies (Fig. 7).

The caudate nucleus and putamen showed moderate loss of nerve cells, the small neurons being mainly affected. The neuronal loss was accompanied by marked astrocytic proliferation and slight fibrous gliosis. The caudate nucleus was fairly uniformly affected at every level while in the putamen the damage was greater in the lateral than in the medial portions. The caudato-putaminal and putamino-pallidal bundles showed severe loss of nerve fibres and the myelin sheaths were poorly stained. The globus pallidus showed slight pallor of myelin. No changes were present in the hypothalamus, thalamus, claustrum, substantia nigra, or amygdaloid nucleus.

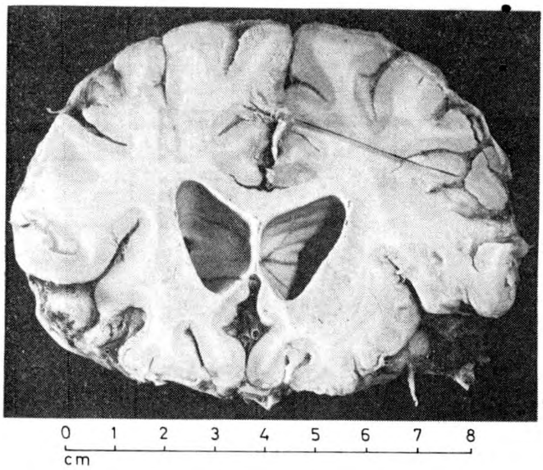

Fig. 7 *Coronal slice of the brain. Note marked shrinkage of the striate body.*

No abnormality was detected in the cerebral cortex or centrum semiovale.

The cerebellar cortex showed moderate loss of Purkinje and granule cells. The inferior olives showed slight loss of nerve cells but otherwise the brain stem was normal. The spinal cord was normal at all levels.

Case 3. This boy was the second child of unrelated white parents. An older brother and a younger sister remain in good health. There is no family history of neurological disease. Pregnancy was complicated by bleeding at 4 months which necessitated hospital observation. Fetal movements may have been diminished. The delivery at term was uneventful. The birthweight was 3·8 kg. He was noted to smile and follow visually at 6 weeks, and he was sitting without support at 3½ months. However, at 9 weeks he had, on the same day, 5 left-sided seizures each lasting 10 min, unassociated with fever. He was admitted to a local hospital where an electroencephalogram suggested a right-sided abnormality with a background of generalised slowing. Approximately one month later, 4 similar attacks occurred. Phenobarbitone was administered but 24 hours later the child had a generalised seizure lasting 20 min. Diphenylhydantoin was added to the treatment but continued left-sided and generalised convulsions necessitated another hospital admission at 4 months of age. Examination at that time showed a rather pale, visually attentive infant who reached for objects without difficulty. His head circumference was at the 50th centile (42 cm). He had normal head control and vocalisation for his age. Hearing appeared intact. The other cranial nerves were also normal. The child preferred to use the right hand. The muscle tone was normal The deep tendon reflexes were slightly brisker on the left. The plantar responses were equivocal. Laboratory investigations included a normal blood count, urine analysis, and serum electrolytes. Blood and urine amino and organic acid pattern was normal. Screening tests for congenital infections including rubella, toxoplasmosis, and cytomegalic inclusion disease were negative. The CSF was normal. An electroencephalogram demonstrated multifocal spike discharges, especially on the right. An air encephalogram was performed which suggested cerebral atrophy.

Continued seizures precipitated readmission at 7 months. His head circumference was 44 cm. The neurological findings were unchanged except that his response to auditory stimuli was less acute than at the previous examination at 4 months. His course continued to be marked by periods of poor control of the seizures.

During the next year he developed complex choreoathetotic movements of all extremities. There was marked hypotonia although the tendon jerks were brisk. The child was developmentally retarded at the 4 months level. His condition remained static until he died at age 2¾ years.

Necropsy

The body was well covered and there was fine hair over the neck, back, arms, and thighs. The head was small, head circumference 45 cm. There was terminal bronchopneumonia. No abnormality was detected in any organ except the CNS.

The brain was reduced in size, the total weight being 810 g, the cerebellum and brain stem accounting for 90 g. (The average weight of normal brain is 1140 g for this age.) No morphological abnormality was noted externally but coronal sectioning showed enlargement of the lateral ventricles which was most pronounced anteriorly. The caudate nucleus was shrunken along its entire length while the putamen appeared to be of normal size (Fig. 8).

Marked loss of neurons was observed in the caudate nucleus, the small nerve cells being affected more than the large ones. The degeneration was accompanied by prominent astrocytic gliosis but only little fibrillary reaction. The process was

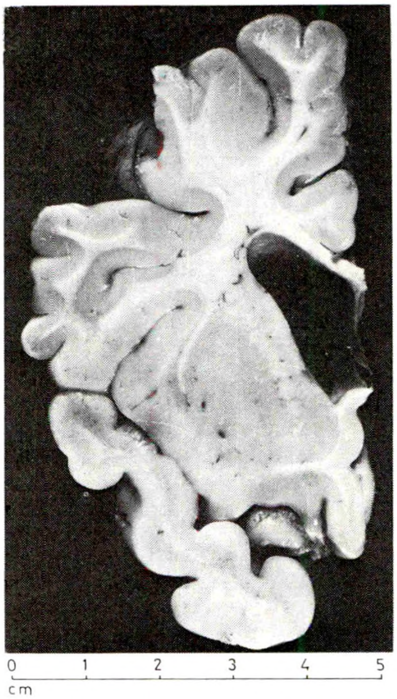

Fig. 8 *Coronal slice of left hemisphere. Note marked shrinkage of the caudate nucleus.*

increasingly severe more caudally. There were also a few microscopical foci of spongy appearance. The putamen on either side showed less marked loss of neurons, but there was obvious proliferation of astrocytes in the dorsal regions. Loss of nerve fibres was noted in the caudato-putaminal bundles. No changes were seen in the thalamus, subthalamic nucleus, globus pallidus, substantia nigra, or mammillary body. The Ammon's horn showed marked neuronal loss and gliosis throughout. The remainder of the cerebral cortex was well preserved. The centrum semiovale was normally myelinated.

There was severe loss of Purkinje and granule cells in the cerebellar cortex with prominent gliosis. The white matter of the folia showed pallor on myelin staining. Slight loss of nerve cells was apparent in the inferior olives. The pons showed a few microscopical foci of recent haemorrhage. There was no abnormality in the spinal cord.

Discussion

The outstanding pathological feature of the 3 cases presented is bilateral striatal degeneration. The histological picture bears the hallmarks of a chronic process—i.e. total absence of a mesodermal reaction and breakdown material in spite of the obvious neuronal loss and astrocytic proliferation.

Degeneration of the striatum is the characteristic lesion in Huntington's disease (Campbell *et al.*, 1961; Jervis, 1963; Markham and Knox, 1965; Byers and Dodge, 1967; Byers *et al.*, 1973). However, Byers *et al.* (1973) reviewing the neuropathological findings in 14 children with Huntington's disease, noted that in addition to the striatal lesion, virtually all reported cases also showed degeneration of the globus pallidus and the cerebral cortex albeit to a less severe degree than that of the striate body. In their own 4 cases which were extensively studied similar damage was detected in the thalamus, pontine tegmentum, vestibular nuclei, and the cerebellum.

Roessmann and Schwartz (1973) described 2 brothers with a subacute progressive neurological syndrome that was characterised by onset in infancy, psychomotor retardation, and rigidity. Pathological examination showed marked neuronal loss in the caudate nucleus and putamen, accompanied by moderate astrocytic proliferation. The rest of the brain was reported as normal.

An apparently distinct entity of necrosis of the striate body has been reported by several authors (Marinesco and Draganesco, 1929; Hawke and Donohue, 1950; Miyoshi *et al.*, 1969). The neurological symptoms began after a febrile illness in childhood. The clinical features included alteration of consciousness and abnormal muscle tone with involuntary movements and, occasionally, myoclonic seizures. Naked eye examination of the brains disclosed softening of the caudate nucleus and the putamen. Microscopically the softened areas were necrotic with brisk mesodermal reaction. Some of the cases were familial.

Verhaart (1938) described striatal necrosis in a series of patients who also showed similar lesions in other regions of the brain, particularly in the basal ganglia and brain stem. It was suggested (Friede, 1975) that his cases may represent an early description of Leigh's subacute necrotising encephalomyelopathy.

The nosological classification of our cases poses considerable difficulty. Pathologically all 3 showed progressive degeneration of the striate body. In Cases 1 and 2 both the caudate nucleus and putamen were severely affected, while in Case 3 only the caudate nucleus showed severe degeneration with a less pronounced lesion in the putamen. Furthermore, the clinical course of Case 3 differed from the others. Cases 1 and 2 were remarkably similar in the juvenile onset of psychiatric symptoms, seizures, dementia, tremor, and rigidity. Case 3, on the other hand, presented at 9 weeks with seizures that were refractory to anticonvulsant therapy. His clinical course was characterised by psychomotor retardation, hypotonia, and choreoathetosis in addition to severe seizures. He died before his 3rd birthday.

Cases 1 and 2 bear notable similarity to Huntington's disease in their clinical course. However, only Case 1 has a positive family history in that her father developed chorea at age 30, six years after the onset of symptoms, and one year after the death of his daughter. In view of this history and the clinical course Case 1 is, in our opinion, a case of juvenile Huntington's disease, in spite of the fact that the neuropathological lesions in her case were more restricted than those in previous reports (Byers *et al.*, 1973). The pathological features of our cases are more similar to those described by Roessmann and Schwartz (1973). The only significant difference is in the cerebellum. However, we feel that the loss of Purkinje and granule cells in the cerebellar cortex may be secondary, caused either by the intractable seizures or anticonvulsant medication (Hoffman, 1958). This would be supported by the neuronal loss and gliosis in the Ammon's horn in Cases 1 and 3. The clinical presentation and course in Cases 1 and 2 were dissimilar from those of Roessmann and Schwartz. Case 3 was similar to their cases in age of onset but seizures, which were so prominent in our patient, were not noted in those of Roessmann and Schwartz. Our cases also differed in that there was no evidence of siblings being similarly affected.

While our Cases 1 and 2 bear clinical similarity to juvenile Huntington's disease with a positive family history in Case 1, the pathology in all 3 patients resembles more closely the cases of striatal degeneration reported by Roessmann and Schwartz. The diagnostic problem is whether all these cases represent a single disease of wide spectrum with the same biochemical defect or whether the clinical and pathological differences are significant and therefore there is more than one disease. The genetic implications make such a distinction important. Huntington's disease is an autosomal dominant disorder whereas the cases of Roessmann and Schwartz suggest an autosomal recessive pattern. The final classification of striatal degeneration has to await the determination of the underlying biochemical defect.

We thank Dr J. Wilson for his advice and permission to publish reports of his patients, and Dr B. E. Kendall for the interpretation of the CAT scan. The histological sections were done by Mrs Jenny A. Taylor, Mrs Jean M. Barron, and Mrs Jane M. Weir. The photographs were produced by Mr N. G. Le Page and Mr R. J. Lunnon.

We also thank Dr W. G. P. Mair for his advice.

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Screening for cystic fibrosis in the newborn by meconium analysis

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SUMMARY During a 4-year routine screening programme for cystic fibrosis (CF) 15 464 specimens were examined for raised meconium albumin levels by a test strip method and by electroimmunoassay. The incidence of false-positive results was about 5 per 1000 specimens in either test. This could be reduced by 90% by determining the ratio of albumin : α-1-trypsin inhibitor (a ratio below 2·0 being considered as a negative result), and it could be reduced to zero by determining the ratio in subsequent faecal specimens. Three of 12 meconium specimens from infants with proved CF gave false-negative results in all 3 tests. The other 9 specimens had >100 mg albumin/g dry weight and albumin: α-1-trypsin inhibitor ratios of >3·0; in subsequent faecal specimens the ratios were over 4·0. 176 meconium specimens from elsewhere in the UK were examined and these included 23 from infants who were subsequently proved to have CF. Six of these 23 CF specimens gave false-negative results, the other 17 being strongly positive. The origins of meconium serum protein suggest that infants with CF in whom meconium gives false-negative results have normal pancreatic functions at birth. The specificity of current meconium tests therefore cannot be improved as they depend on pancreatic dysfunction.

The fact that the prognosis for infants with cystic fibrosis (CF) is improving is probably related to earlier diagnosis of the disease, thus enabling treatment to begin before the onset of irreversible pulmonary changes (Huang *et al.*, 1970; Shwachman *et al.*, 1970; Stern *et al.*, 1976; Orenstein *et al.*, 1977). With the exception of infants born with meconium ileus, the presence of CF in the newborn may not be suspected clinically for some time after birth and irreversible lung damage may have occurred (Warwick, 1969; Shwachman *et al.*, 1970). There is therefore a case for mass neonatal screening for CF in those countries where the incidence of the disease is high.

Although the detection of raised concentrations of ions in the sweat is the most specific and accurate test for CF, for technical reasons this approach is not at present suitable for mass screening (Committee for a Study for Evaluation of Testing for Cystic Fibrosis, 1976). Most neonatal screening tests for CF thus depend on the detection of a raised albumin content in meconium either by the semiquantitative test strip (Stephan *et al.*, 1975) or by other immunochemical methods (Kollberg and Hellsing, 1975; Ryley *et al.*, 1975; Schuttringer and Zinterhofer, 1978). The raised meconium albumin content most probably reflects a reduction in, or even absence of, pancreatic secretions containing proteolytic enzymes.

We report here the results from a 4-year study of CF screening by meconium analysis in which a comparison was made between the Boehringer Mannheim meconium test strip (BM-mec test) and the electroimmunoassay of albumin. The albumin: α-1-trypsin inhibitor (alb: α-1-TI) ratio both in meconium and in subsequent faecal specimens was also assessed for its ability to improve the specificity of screening.

Methods and materials

Collection of meconium and faeces. Meconium specimens were collected daily from the maternity units of the University Hospital of Wales, Cardiff, from December 1973 to November 1977 and from St David's Hospital, Cardiff, from April 1975 to November 1977. During the 4-year period of the study, meconium specimens from home births were sent to the laboratory via the Community

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Midwives Unit. Analysis of 15 464 specimens was carried out, of which 12 specimens were from infants with subsequently confirmed CF. Additional meconium specimens from 176 infants, 23 of whom were subsequently confirmed to have CF, were sent from other hospitals in the UK and were considered separately. Faecal specimens were analysed from 203 infants whose meconium gave a positive result with any test or from infants clinically suspected as having CF.

Collection of cord sera and amniotic fluid. Cord sera matched with the infants' meconium specimens were obtained during a routine screening investigation into α-1-trypsin inhibitor deficiency in the newborn. Amniotic fluid specimens were taken at the University Hospital of Wales, from each mother in whom the pregnancy was thought to carry a high risk of fetal abnormality. Specimens contaminated with blood or from babies in whom a congenital disorder was confirmed were not included in the results. All specimens were collected at an estimated gestation of 16–22 weeks.

Laboratory procedure for studying specimens. Meconium specimens were first tested with the BM mec-test (Boehringer Mannheim GmbH., Mannheim, Germany) and part of each specimen was transferred to a universal container for electroimmunoassay. A 4% wet weight suspension of the specimen in 0·9% sodium chloride was prepared by homogenising the specimen in saline with the aid of a 19 mm diameter Teflon pestle (A. H. Thomas, Philadelphia, USA) driven by a stirring motor at 2000 rev/min (Baird and Tatlock, Essex, UK) for about 10 seconds. A 4% wet weight suspension was approximately equivalent to a 1% dry weight suspension previously used (Ryley *et al.*, 1975). It was found unnecessary to remove the insoluble debris before analysing the protein content by electroimmunoassay. The rest of the specimen was freeze-dried and stored at 4°C for future reference. For purpose of comparison, albumin/g dry weight was estimated for all specimens in which albumin had been detected in the 4% wet weight suspension.

Faeces were not tested by the BM mec-test as the albumin content, even in specimens from infants with CF, was very low. On receipt of the specimen, a 16% wet weight suspension, approximately equivalent to a 4% dry weight suspension (Ryley *et al.*, 1976), was prepared in saline. The suspension was homogenised in a sealed universal container by a vortex mixer. The alb:α-1-TI ratio was determined for all faecal specimens.

BM mec-test for protein in meconium. Specimens were tested with the BM mec-test and the results classified as negative, possible positive, or positive (Ryley *et al.*, 1975).

Quantitative electroimmunoassay. Electroimmunoassay of albumin, α-1-TI, and α-1-CI in meconium and faeces was carried out as described (Ryley *et al.*, 1975, 1976). Protein concentrations in undiluted amniotic fluid and cord sera, diluted 1:20 with barbitone buffer were also estimated by electroimmunoassay.

Results

Comparison of the BM mec-test and electroimmunoassay for albumin. Five infants per 1000 passed meconium specimens that gave a positive or a possible positive result. 34 infants per 1000 passed meconium that contained more than 1 mg albumin/g dry weight and about 5 per 1000 specimens had values in excess of 20 mg/g dry weight. As over 20 mg albumin/g dry weight (5 mg/g wet weight) is usually taken as positive, the false-positive rate was similar in either test (Table 1).

When specimens from infants with CF were tested, 9 were positive and 3 negative in the BM mec-test. The 9 positive specimens all had levels in excess of 100 mg albumin/g dry weight with a mean value of

Table 1 *Comparison of BM test and albumin assay in meconium from normal and CF infants**

	BM test strip result	*Albumin content mg/g dry weight*					
		<1·0	*1–4*	*4–20*	*20–50*	*>50*	
Infants							
Free of CF	−	14 948	212	186	24	—	15 370 (99·47%)
	±	—	—	28	19	—	47 (0·30%)
	+	—	—	3	7	25	35 (0·23%)
		14 948 (96·74%)	212 (1·37%)	217 (1·40%)	50 (0·32%)	25 (0·16%)	15 452
With CF	−	2	—	1	—	—	3
	±	—	—	—	—	—	—
	+	—	—	—	—	9	9
		2	—	1	—	9	12

*Specimens routinely screened in Cardiff between November 1973 and October 1977.

313 ± 145 mg/g dry weight (110–490 mg/g dry weight). Two of the other 3 specimens had <1 mg albumin/g dry weight and the 3rd had 11 mg/g dry weight. Thus all 3 specimens gave false-negative results with both albumin tests (Table 1).

23 meconium specimens from infants with CF were also examined independently of the routine screening programme. 17 gave positive results with the BM mec-test and had >50 mg albumin/g dry weight with a mean value of 283 ± 138 mg/g dry weight (range 78–510 mg/g dry weight). One specimen gave a possible positive result with the BM mec-test and had 34 mg albumin/g dry weight. The other 5 specimens gave negative results with the BM mec-test and had 1·0–17·0 mg albumin/g dry weight.

Evaluation of the alb: α-1-TI ratio. An alb: α-1-TI ratio value was estimated for each specimen that contained >4 mg albumin/g dry weight and for each meconium specimen from an infant with CF, irrespective of albumin content (Table 2). Wherever possible, the ratio was subsequently estimated for faeces. A value of 2·0 was taken as the borderline value between positive and negative results (Ryley *et al.*, 1975). Two specimens contained <20 mg albumin/g dry weight but had ratios of over 2·0. One specimen was from an infant who died a few days after birth and was found at necropsy to have oesophageal atresia without a tracheo-oesophageal fistula. The other was from an infant previously described by us (Ryley *et al.*, 1975) in whom the ratio had been artificially high because the mother had ZZ α-1-TI deficiency. 65 specimens from infants without CF had >20 mg albumin/g dry weight and 9 of these also had a ratio of over 2·0. However the alb: α-1-TI ratios in the subsequent faecal specimens were not higher than 0·2 in any of the 9 infants. Eight of the 9 were premature with estimated gestation ages of between 27 and 33 weeks, and the specimen from the 9th infant was contaminated with blood. 10 other specimens appeared to be contaminated with blood but in none was the ratio above 2·0.

The 9 positive meconium specimens from infants with CF all had ratios of >2·0 with a mean value of 8·2 ± 5·3 (range 3·0–20·0). In all 7 follow-up faecal specimens, the ratio value was >4·0. The 3 negative meconium specimens from infants with CF also had ratios of <0·2; in follow-up studies, faeces from 2 infants gave ratios of 5·1 and 3·5. Faeces from the 3rd infant had a ratio of <0·1 but this child was receiving a pancreatic enzyme supplement to his diet.

18 specimens of meconium from CF infants outside the screening programme had >20 mg albumin/g dry weight and 17 had ratios >2·0 with a mean value of 7·0 ± 3·9 (range 3·0–16·0). The other specimen which had the lowest albumin content of the 18 (34 mg/g dry weight) had a ratio of 0·3.

Five specimens had a low albumin content, 4 had ratios of <0·2 and one, from an infant with meconium ileus, had a ratio of 2·1. In cases where follow-up studies on faeces were possible, all but one specimen had a ratio of >2·0.

In addition to the above, 3 faecal specimens were obtained from infants with CF in whom the meconium had not been screened at birth and all 3 specimens had ratios >3·0. Conversely no faecal specimen from infants in whom CF was initially suspected but not subsequently confirmed, gave ratios higher than 0·15.

False-negative results. Nine of the 35 meconium specimens from all infants with CF gave a false-negative result in at least one of the 3 tests (Table 3). Specimens 1–7 gave a negative result with the BM mec-test, albumin assay, and alb: α-1-TI ratio. Specimen 8 gave a borderline positive result with the test strip and albumin assay, but gave a negative ratio result. Specimen 9 gave negative test strip and albumin results, but a borderline positive ratio. CF was confirmed in Cases 1–8 by the infant having symptoms consistent with the disease and positive results to the sweat test. Case 9, born with meconium ileus, died soon after an operation; the diagnosis of

Table 2 *Distribution of albumin: α-1-trypsin inhibitor ratio in meconium and faecal specimens. Ratio estimation was carried out on specimens from normal infants where albumin content was greater than 4·0 mg/g dry weight*

	Albumin content in meconium specimen	*Albumin: α-1-trypsin inhibitor ratio in meconium*			*Albumin: α-1-trypsin inhibitor ratio in faeces*		
		<1·0	*1·0–2·0*	*>2·0*	*<1·0*	*1·0–2·0*	*>2·0*
Infants							
Free of CF	4–20	219 (1)	6 (4)	2 (1)	6	—	—
	20–50	27 (3)	7 (3)	6 (6)	12	—	—
	>50	12 (3)	10 (4)	3 (3)	10	—	—
With CF	0–20	3 (3)	—	—	1	—	2
	20–50	—	—	—	—	—	—
	>50	—	—	9 (7)	—	—	7

Figures in brackets indicate number in each group for whom follow-up faecal specimen was examined.

Table 3 *Data on CF infants who passed meconium that gave a false-negative result*

Case	*Age at diagnosis (months)*	*Sibling of older CF child*	*Sweat Cl (mmol/l)*	*Meconium tests*			*Faeces tests*	
				BM test strip	*Albumin mg/g dry weight*	*Albumin: α-1-trypsin inhibitor ratio*	*Albumin mg/g dry weight*	*Albumin: α-1-trypsin inhibitor ratio*
1	10	No	110	—	<1·0	—	5·0	3·6
2	3	Yes	120	—	8·4	0·1	5·0	5·0
3	5	Yes	100	—	17·6	0·22	4·3	4·0
4	3	No	110	—	10·8	0·17	17·6	13·2
5	5	Yes	90	—	1·1	0·01	12·0	15·0
6	9	No	105	—	<1·0	—	<0·1	—
7	1·5	Yes	120	—	2·6	0·02	1·2	1·7
8	6	Yes	110	±	34	0·3	Not done	
9	1 week	No	*	—	11	2·1	Not done	

*Diagnosis of CF made on evidence of meconium ileus and at necropsy.

CF was confirmed at necropsy. Where faeces were collected, only 2 infants' specimens had a ratio $<4{\cdot}0$. In one, the infant was receiving pancreatic enzyme supplement and, in the other, the infant had been diagnosed early by a sweat test before symptoms became apparent. The sweat test was carried out, despite a negative meconium result, because the infant was known to be at risk. Five of the 9 infants were younger siblings of children with CF. Three of the 4 other infants (Cases 1, 4, and 6) had older normal siblings but all 3 mothers had had previous miscarriages.

Distribution of protease inhibititors in meconium, cord serum, and amniotic fluid. As the protease inhibitors in meconium are resistant to proteolysis, their distribution in meconium should be similar to their distribution in the major source of meconium serum protein whether it is amniotic fluid or vascular transudates. The distributions of protease inhibitors were estimated in 55 normal and 26 CF meconium specimens, in 55 cord sera and 50 amniotic fluids, and the α-1-TI: α-1-CI ratios were calculated (Table 4). The cord sera came from the same neonates as the normal meconium specimens. Although the concentration of the protease inhibitors in meconium from infants with CF was lower than in specimens from normal infants, the proportion of α-1-TI to α-1-CI in the two groups was not significantly different ($P>0{\cdot}2$). The α-1-TI : α-1-CI ratio in amniotic fluid was similar to that in normal or CF meconium (in both $P>0{\cdot}2$), but the α-1-TI : α-1-CI ratio (33·1) in cord sera was significantly higher than the ratio in meconium ($P<0{\cdot}001$).

Table 4 *Distribution of protease inhibitors in meconium cord serum, and amniotic fluid*

	No.	*α-1-TI*	*α-1-CI*	*α-1-TI: α-1-CI*
Meconium				
From normal infants	55	71·7±32·0 mg/g	7·4±4·4 mg/g	12·7±10·1
From infants with CF	26	54·0±31·0 mg/g	3·8±2·6 mg/g	15·2±4·4
Cord serum from normal infants	55	281±73·0 mg/100 ml	12·3±8·5 mg/100 ml	33·1±26·6
Amniotic fluid	50	23·0±9·8 mg/100 ml	1·7±0·8 mg/100 ml	14·7± 5·3

Conversion: traditional units to SI—α-1-trypsin inhibitor: 1 mg/100 ml ≈ 0·01 g/l

The α-1-TI and α-1-CI content was estimated in 2 other meconium specimens not included in the analysis. The 1st was from an infant born to a mother with ZZ α-1-TI deficiency in whom the amniotic fluid would also be α-1-TI deficient. The ratio between the 2 protease inhibitors is 1·6:1. The infant's α-1-TI was typed as MZ and the α-1-TI: α-1-CI in the cord serum was 12·8:1. The 2nd specimen was from a child with oesophageal atresia without a tracheo-oesophageal fistula and in whom the specimen was unlikely to have amniotic fluid. The α-1-TI concentration was 6 mg/g dry weight but only trace amounts of α-1-CI could be detected in a 4% aqueous extract.

Discussion

BM mec-test strip compared with albumin immunoassay. There was little difference in specificity between the BM mec-test and the albumin assay. The test strip is quicker and simpler and can be carried out in the wards. However, if it is used by untrained personnel, it is likely that a higher incidence of false-positive results will be obtained than the 0·5% reported in this investigation. An overall false-positive rate of between 1 and 2·5% of all specimens screened has been reported (Stephan *et al.*, 1975; Schuttringer and Zinterhofer, 1978).

The albumin electroimmunoassay done in this laboratory gives a quantitative rather than a qualitative result; this result is obtained within half a day rather than the 24–48 hours needed for immunodiffusion. In specimens containing >20 mg albumin/g dry weight, an alb: α-1-TI ratio can be determined in the meconium and subsequent faecal specimens. Such a procedure reduces the false-positive results to a negligible number and, at the same time, confirms positive results. A quantitative albumin estimation may also be combined with limited sweat testing to reduce the number of false-negative results. This suggestion is based on the observation that in this study, 7 of the 9 false-negative specimens contained more than 1 mg albumin/g dry weight. Kollberg and Hellsing (1975) also reported that the 2 false-negative specimens in their study each contained >1 mg albumin/g dry weight. A sweat test for those infants in whom the meconium contained >1 mg albumin/g dry weight would mean testing about 34 infants in every 1000 live births, and such infants could be tested on their first clinic attendance. A sweat test should be done earlier if the meconium specimen is positive and the ratio remains positive in the stool; it should also be carried out if the child is a sibling of a known case. The high incidence of false-negative specimens from younger siblings of known CF children found in this study means that no reliance should be put on negative meconium test results from such children.

The cost of the 2 tests is difficult to determine because there are so many variables. The cost of material for the albumin immunoassay, provided the antiserum is prepared in the laboratory, is about one-10th that of the material for the BM mec-test; one penny per test compared with 10 pence per test. If commercial antiserum is used the cost of the albumin assay increases almost 3-fold. It is not possible to assess the cost of labour for the 2 tests as the salary of the investigator varies. In our laboratory, the time for testing 10 specimens by the BM mec-test was 5 min compared with 25 min for the albumin assay; the time of development of both tests was not included. Thus the labour costs are at least 5-fold higher with the albumin immunoassay and, consequently, the total cost for either test is similar.

Origins of false-positive and negative results obtained with meconium screening. Identification of the source of serum protein and particularly albumin in meconium is important if one is to explain the reasons for false-positive and false-negative results and consequently determine if it is possible to improve the specificity of the test. There is no definite evidence on the major source of albumin and other serum proteins in meconium but the consensus is that most of it comes from ingested amniotic fluid (Schutt and Isles, 1968; Prosser *et al.*, 1974; Ryley *et al.*, 1975), rather than from transudates into the gut from the fetal vascular system. The findings concerning the distribution of inhibitors in meconium, cord serum, and amniotic fluid support this view.

If amniotic fluid is the main source of meconium serum protein, the final concentration of albumin almost certainly reflects pancreatic enzyme activity but if there is a large contribution of protein from the fetus, it could be argued that raised meconium albumin concentrations in CF may reflect an increase in the intestinal transudation (Wiser and Beier, 1964; Rule *et al.*, 1970), especially from the lower part of the gut where proteolytic activity may be less. The results in this study show that serum protein originates from the same source in meconium specimens from healthy neonates and infants with CF, and are consistent with the suggestion that vascular transudates do not contribute substantially to the final protein content of meconium. Thus a raised albumin content in meconium from CF infants signifies deficient pancreatic enzyme activity in the fetal gut and similarly a false-negative meconium test means that the specimen was passed by an infant with CF who had normal pancreatic function at birth.

Those infants without CF who pass meconium with a raised albumin content could have reduced pancreatic function at birth. Gitlin *et al.* (1972) reported that before birth, a fetus daily ingests half the total volume of amniotic fluid and consequently as amniotic fluid volumes vary, so also does the amount of ingested protein from child to child. Reduced intestinal proteolytic activity coupled with a higher than average protein intake might lead to a final raised meconium albumin content. This would explain why the alb: α-1-TI ratio is effective in reducing false-positive results. The ratio compares the concentration of a protein liable to proteolysis, albumin, with the concentration of a protein resistant to proteolysis, α-1-TI. Thus the concentration of α-1-TI in meconium directly reflects the initial protein intake and will be high or low accordingly. The concentration of albumin, on the other hand, depends not only on its initial concentration but also on the extent of its proteolysis. A high initial albumin concentration together with reduced proteolytic activity may result in a specimen giving a positive albumin result. A specimen from another infant with the same reduced gut enzyme activity but in whom the initial albumin intake was low, may give a negative albumin result. The ratio in both specimens however will be similar.

Contamination by occult blood has been suggested as an alternative explanation for false-positive results, especially in preterm births (Griffiths *et al.*, 1976), because of the observation that many specimens containing albumin also gave a positive guaiac test. At the start of our study, we routinely tested 1% meconium extracts for occult blood with the Hema-Combistix (Ames Company, Bucks, England) which used the o-toluidine-peroxidase reaction for haem. The test was stopped after positive results were obtained with the first 100 specimens, only 2 of which contained any albumin. The specificity of the 2 tests is similar although the test stick is probably more sensitive than the guaiac test (Makarem, 1974). It is therefore not clear at the moment how important contamination by occult blood is in the generation of false-positive results.

CF screening

This study shows that current meconium tests for CF which appear to depend on the status of pancreatic function will miss about 25% of infants with the disease. If for any reason CF is suspected, little reliance should be put on a negative meconium test. Also any new test should be assessed according to what effect the presence or absence of proteolytic activity will have on the component being measured, as specificity will be increased only if it can be shown that there are changes in meconium composition caused by the underlying genetic lesion but independent of pancreatic activity. Such changes, if present, will probably be found in the mucin component of meconium.

The final assessment on whether screening for CF should become routine will depend not only on the specificity of tests but on the results of long-term treatment in cases where this was initiated soon after birth. If a better prognosis is related to early detection, even a test that detects 75% of affected children will contribute to the management of the disease when linked to a programme of treatment. In our opinion such studies are feasible with current meconium screening methods.

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Curd and whey proteins in the nutrition of low birthweight babies

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SUMMARY Some animals thrive more satisfactorily on a milk that contains whey and curd protein. For this reason human milk protein (which contains about 40% whey) may have some advantages over cows' milk protein (which contains about 15% whey) and so infants feeding formulae based on demineralised whey in which the protein has been modified to achieve a curd:whey ratio similar to that in human milk may also thrive more satisfactorily. As the exact situation in the human newborn is unclear, the effects of feeding a formula containing unmodified cows' milk protein (mainly curd) and one containing the same amount of modified cows' milk protein (curd and whey) were studied in 57 low birthweight babies during the first 3 months of life. During the early weeks of life the curd and whey group grew bigger, absorbed more nitrogen, and excreted proportionately less urea. These results suggest that a curd *and* whey formula has advantages in the protein nutrition of low birthweight babies, especially the preterm ones. We feel it would be unwise to reduce the protein content of a formula based on cows' milk below 15 g/l unless it was modified to achieve a larger proportion of whey protein and hence, among other qualities, more cysteine. Although some of the qualities of human milk protein can be mimicked by the use of demineralised whey formulae, others cannot.

Some animals thrive more satisfactorily on a milk that contains whey and curd protein, but the significance of this for the human baby is unclear. It is relevant to re-examine this point because of recent trends in infant feeding practice.

Whey protein (lactalbumin) is more effective in promoting the growth of rats, dogs, mice, and chicks than curd protein (casein) (Mueller and Cox, 1947); it is also more effective in regenerating the plasma albumin of protein-depleted dogs (Chow *et al.*, 1948), and in rats it has a higher 'biological value'—that is, retention of absorbed nitrogen is greater (Tomarelli and Bernhart, 1962). The significance of these observations for the human baby is not known. Empirically cows' milk protein (containing <15% of whey protein compared with >40% in human milk protein) has for many years been used with satisfaction for infant feeding; growth velocities of babies receiving a predominantly curd protein formula were similar to those receiving a curd and whey formula (Natelson *et al.*, 1955; Barness *et al.*, 1963), and nitrogen retention on cows' milk was similar to that of human milk (Waterlow *et al.*, 1960).

The Medical Research Council and Agricultural Research Council (1974) drew attention to two recent changes in the understanding of protein metabolism. Firstly, although the effective amino-acid patterns of human and cows' milk protein may be similar, the nutritive value of milk proteins does not depend only on the component amino-acids—e.g. the absorption of intact peptides by the intestine indicates that proteins of similar amino-acid pattern might, nevertheless, be handled quite differently. Secondly, a developmental deficiency in the newborn of the liver enzyme cystathionase may prevent adequate conversion of the high methionine content of curd protein into cysteine, so limiting nitrogen retention and making cysteine—an essential amino-acid for the newborn (Gaull *et al.*, 1972).

Empirically two trends in infant feeding make it relevant to reinvestigate the matter. Firstly, the reduction in protein concentration of infant feeding formulae to 1·5–1·8 g per 100 ml—i.e. well below that in cows' milk—makes consideration of protein

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quality in these formulae more important than when most babies received formulae containing about 3·5 g cows' milk protein per 100 ml. The Department of Health and Social Security (1974) stated that the lower protein formulae should supply the 'essential amino-acids in amounts at least equal to those in an equal volume of breast milk'. More importantly, however, formulae based on demineralised whey are now available—such as Gold Cap SMA-S26, Osterfeed, and Cow and Gate Premium. One advantage of these formulae is their lower mineral content but, in addition, the curd:whey protein ratio has been altered to a value similar to that of human milk. This has a teleological appeal but it is unclear whether it has any other advantages.

For these reasons we studied the nutritional effects of curd and whey protein by comparing babies fed on two formulae: one based on demineralised whey with a curd:whey ratio similar to that in breast milk (group 1) and one containing unmodified cows' milk protein—i.e. mainly curd protein (group 2).

Patients and methods

Formulae. Fig. 1 gives details of the formulae used. The curd and whey formula was based on Gold Cap SMA-S26, and the curd formula was SMA. They were manufactured in special batches for this study by the manufacturer, John Wyeth, and the fat blend was identical. The main difference was the quality of the protein—predominantly curd protein in SMA given to group 2; curd *and* whey protein in the S26 given to group 1. However, as a result of the demineralisation process, the sodium and potassium concentrations in S26 were lower than those in SMA (Table 1). At reconstitution of the feeds, therefore, extra sodium (5 mmol/l as citrate) and extra potassium (4 mmol/l as citrate, 2 mmol/l as chloride) were added to the S26 to bring the concentrations of sodium, potassium, and chloride up to those in SMA. Citrate and chloride were chosen as the other anions because they are the main milk anions (Jenness and Sloan, 1970) and also because this combination lessened the differences in the electrolyte concentrations and acid base characteristics of the two formulae. There were still differences however; although the buffering capacity was similar, the pH was higher while the titratable acidity was lower than in the curd formula; we were unable to devise any method of eliminating this difference without introducing others. There was one other (unwanted) difference between the two formulae. The curd and whey formula contained less calcium and phosphate, thus partly reflecting its lower casein content (Jenness and Sloan, 1970).

Table 1 shows the composition of the reconstituted formulae and also the composition of human milk and unmodified cows' milk. In the curd and whey formula only 41% of the nitrogen was casein, so it contained more cysteine than the curd formula in which 82% of the nitrogen was casein.

Patients. Table 2 gives details of the patients. Beginning in January 1974 all low birthweight babies weighing 1·75–2·26 kg admitted to the special care baby unit of the Sorrento Maternity Hospital, entered the study if their mothers were unable to provide breast milk and had given their informed consent. Babies with severe respiratory distress requiring more than 40% ambient oxygen and not able to tolerate tube feeding were not studied.

Feeding regimen. The first feeds were given within 4 hours of birth to babies nursed initially at the optimum environmental temperature (Hey, 1971), subsequently aiming to maintain rectal temperature at 36·5–37·5°C. Indwelling polyvinyl intragastric

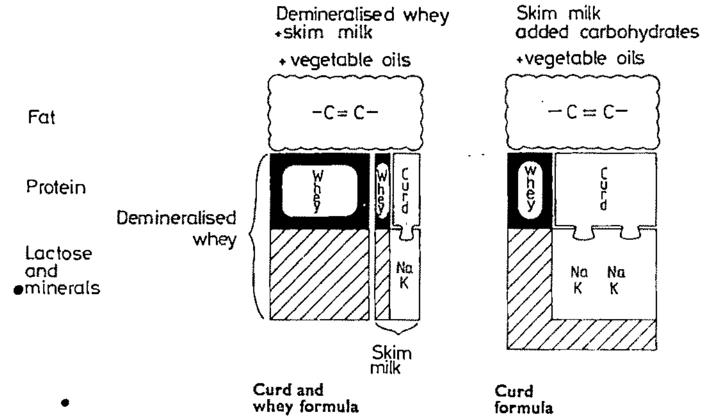

Fig. 1 *The constituents of the demineralised whey formulae and the curd formula.*

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Table 1 *Constituents of curd and curd whey formula, mature human breast milk and unmodified cows milk (per litre whole milk)*

Constituent	*Milk*			
	Curd formula	*Curd whey formula*	*Human**	*Cows**
Protein (N × 6·37) g	15·0	15·0	12·0	33·0
% casein (of total N)	82	41	31·7	80·0
whey (of total N)	13	44	48·2	16·3
nonprotein nitrogen	5	15	20·0	5·8
of energy	9	9	7	20
Amino-acids (mmol/l)				
Cysteine mmol	0·8	2·0	2·4	2·4
mg per 100 kcal	16	38	43	43
Methionine mmol	2·49	2·49	1·54	5·83
mg per 100 kcal	60	60	34	130
Fat g	36		38	37
% of energy		48	51	51
Lactose g	7		7	4·8
% of energy	43		42	29
Energy KJ	2814		2814	2772
Minerals mmol†				
Sodium	12·0 (7·0)		6·5	25·0
Potassium	20·0 (14·0)		14·0	35·5
Calcium	14·0	10·5		
Magnesium	2·5	2·1		
Chloride	14·0 (12·0)		12·1	29·0
Phosphate	14·2	10·6	4·8	31·0
Acid base‡				
pH	6·75	7·15 (6·90)	7·22	6·70
Buffering capacity	1·0	1·0 (0·9)	0·64	2·4
Titratable acidity	1·85	0·60 (0·93)	0·22	3·30

*Derived from Macie and Kelly (1961).

†Figures in parentheses are values before adding electrolyte.

‡Derived experimentally (Berger *et al*., 1978).

Buffering capacity: ml 0·1 mmol/l hydrochloric acid to lower pH to 5·5; titratable acidity: ml 0·25 mmol/l sodium bicarbonate to raise pH to 7·45.

Table 2 *Details of babies*

Babies	*Feeding formula*	
	Curd	*Curd and whey*
Number		
Starting trial	37	33
Withdrawn in first 21 days	8*	5†
Number		
Completing 21 days	29	28
Gestation (completed weeks)‡		
Mean ± SD	36·2 ± 2·1	36·3 ± 2·0
Range	(33–40)	(33–40)
Preterm	16	17
Term	13	11
Male	18	15
Asian	6	10
Number completing 90 days§§	12	12

*Lactation established 1, severe RDS 1, IV treatment for hypoglycaemia 1, parenteral antibiotics 2, convulsion 3.

†Lactation established 2, early discharge possible 1, parenteral antibiotics 2.

‡Determined from reliable maternal dates or method described by Dubowitz *et al*., 1970.

§§Left trial after 21 days: 21 did not keep to trial formulae for various reasons, 12 did not attend for follow-up.

tubes were used if necessary. Appropriate weight-for-dates babies (weight 10-90th centile for gestation, Gairdner and Pearson, 1971) received 40 ml/kg during the first 24 hours of life, the volume increasing by 20 ml/kg each day, reaching 200 ml by the 9th day. Small-for-dates babies (weight < 10th centile) received 60 ml/kg on the 1st day, increasing by 30 ml/kg each day, reaching 200 ml by day 6. Thereafter, the volume remained at 200 ml/kg per day until day 21, after which the mothers were advised to give approximately 200 ml/kg per day according to appetite. For volume calculations, birthweight was used until this had been regained and then the volume was recalculated after each twice-weekly weighing. Plasma bilirubin concentrations exceeded 170 μmol/l (9·9 mg/100 ml) in 11 of group 2 and in 14 of group 1, so extra sterile water (30% of the above volume) was given to each baby until the bilirubin level had fallen to 170 μmol/l for 24 hours. As plasma bilirubin concentrations exceeded 250 μmol/l (14·6 mg/100 ml) in 3 babies in group 2 and 6 in group 1, these babies received phototherapy until these levels were below 220 μmol/l (12·9 mg/100 ml).

Method of assessment and analysis.

Anthropometry

This was performed at birth and at intervals thereafter by H.M.B. (Weight: Salter spring balance; length: Harpenden neonatometer; head and midarm circumference: steel tape measure; skinfold thickness: Harpenden skin calipers.

Plasma biochemistry

Samples of blood were collected by heel prick on days 2, 7, 11, and 21, four hours after the 6 a.m. feed. On days 60 and 90 parents were asked to give no milk for 8 hours before arrival but to give dextrose water as necessary.

The samples of blood were spun down within one hour and the plasma separated and stored at −20°C until analysis as follows: albumin (Northam and Widdowson, 1967), urea by application of the Berthelot reaction after enzymatic hydrolysis with urease, calcium (Baginski *et al*., 1973), and phosphate (Itaya and Ui, 1966).

Nitrogen balance and partition

24-hour samples of urine were collected from 17 baby boys on days 3, 10, and 19. Collection was made directly into a polyethylene container kept on ice and containing one thymol crystal. The urine was deep frozen until it was analysed for uric acid (Caraway, 1955), amino nitrogen (Goodwin, 1970), total nitrogen (Shahinian and Reinhold, 1971), urea and creatinine by standard autoanalyser methods.

Nitrogen balances were performed (Fomon, 1974) on 7 baby boys in each dietary group for 3- or 5-day periods ending on day 21 (group 1 compared with group 2 mean and SD: birthweight 2·06 ± 0·16 compared with 2·04 ± 0·16 kg; gestation 36 ± 2·1 compared with 36 ± 2·5 weeks). The total nitrogen in the formulae, urine, and faeces was determined by the method of Shahinian and Reinhold (1971).

Results

Clinical. Three of the babies in group 2 had convulsions in the first 2 days, and were withdrawn from the trial (Table 2). Neither was hypocalcaemic or hypoglycaemic but they both had low Apgar scores. Many babies did not complete 3 months, mainly because they were also receiving solid foods (usually wheat cereal). Both infant feeding formulae were well accepted with no undue vomiting, abdominal distension, or diarrhoea.

Anthropometry (Table 3). At birth the two groups of babies were similar in size apart from a slightly greater head circumference in group 1. By 21 days these babies had also become heavier and longer. This significant difference in weight gain was present in the preterm babies but not in the term light-for-dates babies (Fig. 2).

By day 90 the difference in growth was no longer significant in the small number of babies that remained in the trial. There were no differences at any age in mean skinfold thickness (using biceps, triceps, subscapular, umbilical, and quadriceps measurements) and mid upper arm muscle circumference (Gurney and Jelliffe, 1973), so the results are not given.

Plasma biochemistry (Table 4). Group 1 babies were less acidotic on days 7, 11, and 21 (these differences

Table 3 *Anthropometry from birth to day 90 in the babies on curd, and curd and whey formulae.*

Measurement (mean ± SD)	*Birth*	*Day 21*	*Day 90*
Number of babies			
Curd	29	29	12
Curd and whey	28	28	12
Weight (g)			
Curd	2051 ± 156	2304 ± 204	4486 ± 342
Curd and whey	2091 ± 107	2430 ± 140	4728 ± 417
P*		<0·01	
Length (cm)			
Curd	45·2 ± 1·4	47·1 ± 1·4	56·0 ± 1·5
Curd and whey	45·7 ± 1·0	47·9 ± 1·1	56·4 ± 1·3
P		<0·05	
Head circumference (cm)			
Curd	31·1 ± 0·9	32·9 ± 1·1	38·3 ± 1·1
Curd and whey	31·6 ± 0·6	33·5 ± 0·9	39·1 ± 1·5
P	<0·02	<0·05	

*P shows significance of difference between the means of the two groups using independent *t* test; values >0·10 not shown.

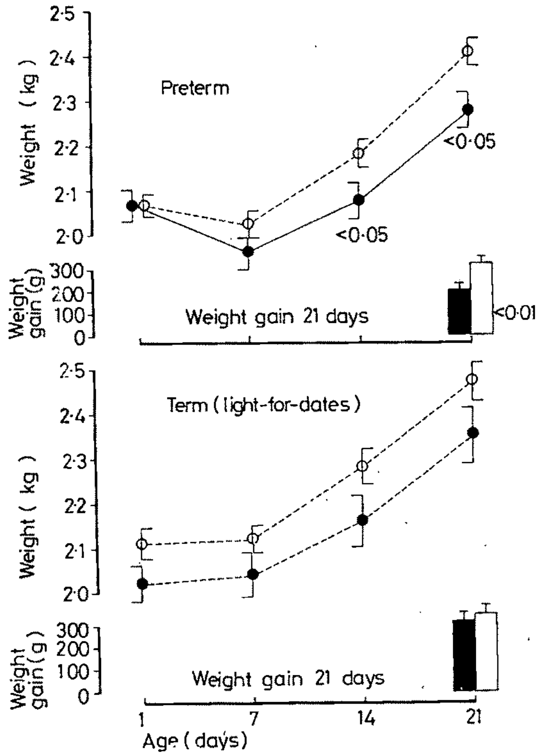

Fig. 2 *Weight gain (mean ± SEM) in preterm and term light-for-dates babies fed on curd (●) and curd and whey (O) formula. A greater increase in weight was found in the preterm but not the term light-for-dates babies fed on the curd and whey formula.*

Table 4 *Blood acid base status*

	Day 2	*Day 7*	*Day 11*	*Day 21*
pH				
Curd	7·42±0·03 (26)	7·41±0·04	7·40±0·07	7·45±0·04
Curd and whey	7·43±0·03 (23)	7·44±0·04	7·44±0·03	7·47±0·05
P		<0·02	<0·01	≈0·08
Carbon dioxide (kPa)				
Curd	4·66±0·93 (26)	3·99±0·93	3·99±0·80	4·12±0·67
Curd and whey	5·32±0·80 (23)	4·66±0·67	4·52±0·80	4·39±0·80
P	<0·02	<0·01	<0·05	
Base excess (mmol)				
Curd	1·2± 2·7 (26)	−3·1±2·8	−3·9±3·7	−0·6±2·8
Curd and whey	2·1± 2·3 (23)	0·6±3·0	0·4±3·0	2·2±2·9
P		<0·001	<0·001	<0·001

Conversion: SI to traditional units—carbon dioxide 1 kPa ≈ 7·5 mmHg.
P significance of difference between means using independent *t* value P>0·10 not shown. Numbers in parentheses are numbers of babies studied when fewer than 27 on any day.

had disappeared by days 60 and 90, so these results are not given). There was no correlation between base deficit on day 11 and weight gain during the first 3 weeks of life ($r = 0 \cdot 34$). There was no difference in plasma concentration of albumin, urea, calcium, and phosphorus throughout the 90-day study period, so the results are not given.

Nitrogen balance and partition (Table 5; Fig. 2). Group 1 babies absorbed a significantly greater proportion of the ingested nitrogen; mean nitrogen retention was higher but not significantly so. These babies excreted less urea nitrogen in the urine (day 10) and had higher urinary urea nitrogen:total nitrogen ratios (Fig. 3).

Table 5 *Nitrogen balance and urine urea excretion (mean ± SD) of babies receiving curd, and curd and whey formulae* ($mmol/kg^{-1}\ 24h^{-1}$)

Nitrogen	*Formulae*		*P**
	Curd (*n* = 7)	*Curd and whey* (*n* = 7)	
Intake (I)	35·3 ± 1·1	35·5 ± 1·6	
Faeces (F)	3·1 ± 1·0	2·3 ± 0·7	<0·03
Urine (U)	10·3 ± 3·2	9·9 ± 2·3	
Absorbed (I-F)	31·9 ± 1·4	33·1 ± 1·5	
Absorption as % of intake	90 ± 3	93 ± 1	<0·03
Retention (I-F-U)	21·5 ± 3·4	23·2 ± 1·1	
Retention as % of intake	61 ± 9	65 ± 5	
Urinary urea nitrogen	(n = 9)	(n = 8)	
Day 3	2·07 ± 0·57	1·76 ± 0·43	
Day 10	2·69 ± 0·77	1·87 ± 0·31	<0·05
Days 19	3·70 ± 1·52	3·76 ± 1·28	

*P, significance of difference between means using Mann Whitney U test values >0·10 not shown.

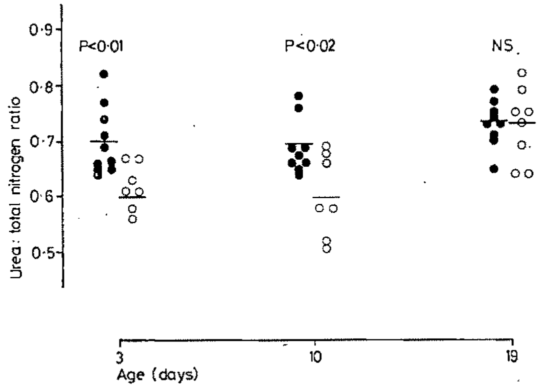

Fig. 3 *Urinary urea nitrogen: total nitrogen over 3 weeks. In the curd and whey group (○) the urea: total nitrogen ratio was lower on days 3 and 10 than in the curd group (●).*

Discussion

During the early weeks the babies in group 1 grew bigger (particularly if preterm), absorbed more nitrogen, and lost less nitrogen as urinary urea.

Were these differences in growth and nitrogen metabolism due solely to the quality of the dietary protein? There were also differences in the acid base qualities of the formulae and indeed the babies in group 1 were significantly less acidotic.

Differences in the acid base status due to the protein quality were expected (Kildeberg and Winters, 1972) and, since addition of the citrate salts to the curd and whey formula equalised the potential base in the formulae, it is probable that the differences in the base deficits were caused by the dietary protein. A lower incidence of metabolic acidosis in babies fed a curd and whey formula was also found by Räihä *et al.* (1976) in studies on protein quality. Whatever the cause, however, it is unlikely that these acid base findings explain the differences in growth; there was no correlation between base excess and weight gain; the degree of acidosis was generally mild, and only 4 babies had base deficits great enough to be diagnosed as late metabolic acidosis (Svenningsen and Lindquist, 1973); Heird *et al.* (1976) suggested that acidosis affects growth by limiting appetite but in our study babies received a prescribed volume of feed.

It seems that the differences in growth velocity and nitrogen metabolism were at least primarily related to the difference in the quality of the dietary protein.

We are uncertain which of the various qualities of whey protein accounts for these differences. Whey protein leads to quicker gastric emptying and a lower intestinal buffering capacity than curd protein (Platt, 1961; Bullen and Willis, 1971) and this may be connected with the higher nitrogen absorption in group 1, but the differences in growth and nitrogen balance may be related to the higher cysteine content of whey protein (Table 1). The curd and whey formula supplied almost as much cysteine per unit volume and energy as breast milk and, unlike the curd formula, meets the estimated cysteine requirements of 23 mg per 100 kcal (45 μmol per 100 kJ) suggested by Fomon *et al.*, 1973. The differences in growth observed by us were not confirmed by others. Barness *et al.* (1963) found other biochemical differences but felt these had no clear advantage, although Räihä *et al.* (1976) concluded that the babies on a curd and whey formula paid a smaller 'metabolic price' to obtain their growth.

Clinical implications. Although the curd and whey formula had nutritional advantages, particularly in the preterm babies, these advantages were marginal. However, curd formulae containing 15 g/l of unmodified cows' milk protein provide less cysteine than does breast milk. If the protein and, therefore, cysteine content were further reduced to lower the renal solute load, then we suspect the reduction in growth velocity might be more pronounced than we observed. We consider it would be unwise to reduce the protein content of an infant feeding formula based on cows' milk below 15 g/l unless the protein was modified so that it included more whey protein. This caution is emphasised by susceptibility of cysteine to damage in the manufacturing processes (Pieniazek *et al.*, 1975).

Although the protein in the curd and whey formula was modified to resemble that of breast milk, nevertheless, it is still cows' milk protein. For example, the whey fraction contains lactoglobulin, more immunogenic than casein (Lebenthal, 1975), and very little lactoferrin; the curd fraction contains K casein which forms micellar complexes with certain minerals, accounting for their higher content in cows' milk (Jenness and Sloan, 1970). Cows' milk contains very little free taurine.

The babies were looked after by Miss A. Frogbrook and I. Sallis and their staff; Mrs J. King and Mrs S. Doughty helped to collect specimens and analysed the results; the Department of Medical Illustration, Birmingham Children's Hospital produced the figures, H. M. Berger held a Sheldon Clinical Research Fellowship of the West Midlands Regional Health Authority and later the Mary Crosse Research Fellowship; John Wyeth gave other financial support. We are grateful to all of them and to Mrs H. Bird and Mrs P. Cox for secretarial assistance.

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Effect of tolazoline in severe hyaline membrane disease

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SUMMARY Tolazoline hydrochloride was given as a pulmonary vasodilator to 20 preterm infants with severe hyaline membrane disease requiring mechanical ventilation who developed persistent severe hypoxaemia. The drug was only given when deterioration persisted despite changes in ventilation techniques and thus there were no control infants. A significant improvement in arterial oxygenation was observed, particularly in those infants without intracranial haemorrhage or pneumothorax. Nine of 10 infants who had an obvious clinical response to tolazoline survived, whereas only 2 survived out of 10 who failed to respond, both being subsequently shown to have pneumothoraces. There appears to be a place for the use of tolazoline in a severely hypoxaemic infant with hyaline membrane disease who is being ventilated and in whom arterial oxygenation cannot be improved by further increase in the inspired oxygen concentration or by alteration of ventilator settings, provided pneumothorax has been excluded.

The normal increase in pulmonary vascular resistance in response to hypoxaemia occurs in an exaggerated form in the newborn infant. Pulmonary artery pressure rises to systemic levels with the reappearance of a transitional pattern of circulation (James and Rowe, 1957; Rudolph and Yuan, 1966). In infants with severe hyaline membrane disease, this response increases the right-to-left shunting of blood leading to increasing hypoxaemia, which is unresponsive to either increases in the fractional inspired oxygen concentration (F_{IO_2}) or to alterations in mechanical ventilator settings (Chu *et al.*, 1967; Stahlman *et al.*, 1972; Gersony *et al.*, 1976). Tolazoline hydrochloride has been suggested as a therapeutic agent for dilating the pulmonary arteries which might be used to improve arterial oxygenation (Cotton, 1965; Korones and Eyal, 1975; Goetzman *et al.*, 1976). This report describes our experience with the use of tolazoline in 20 consecutively admitted infants with severe hypoxaemia due to hyaline membrane disease.

Patients and methods

Twenty critically ill preterm newborn infants with severe hyaline membrane disease born between October 1976 and July 1977, developed persistent severe hypoxaemia while being mechanically ventilated, and were given 48 doses of tolazoline. The clinical details of the infants are shown in Table 1. None of the infants had polycythaemia or hypoglycaemia, and all were managed by methods previously described (Blake *et al.*, 1973). Six babies had coagulation abnormalities, 4 disseminated intravascular coagulation, and 2 had less specific abnormalities. Two infants had severe rhesus isoimmunisation requiring exchange transfusions.

The infants were all ventilated via an oroendotracheal tube with a constant flow pressure-controlled ventilator (Bourns BP 200). Mean peak airway pressure (PAP) was 29 cm (range 20–40) H_2O; mean end expiratory pressure (EEP) was 3·5 cm (range 0–5) H_2O; median inspiration/expiration ratio (I/E ratio) 1:1 (range 1:2–3:1); mean respiratory frequency (f) 30/min (range 25–40/min).

Seventeen infants had umbilical artery catheters sited in the lower abdominal aorta. Fifteen of the catheters had oxygen electrodes at their tips (Searle), allowing the continuous monitoring of arterial oxygen tension (Pa_{O_2}) (Conway *et al.*, 1976). In all infants, frequent blood–gas analyses were performed* on arterial samples obtained from either the arterial catheters or peripheral arteries.

The indication for giving the first dose of tolazoline was deteriorating hypoxaemia in the presence of an inspired oxygen concentration of 100% ($F_{IO_2} = 1{\cdot}0$) and the failure to respond to various manipulations of ventilator settings intended to raise Pa_{O_2} (Blake *et al.*, 1973; Herman and Reynolds, 1973). In 10 infants the Pa_{O_2} was less than 20 mmHg, in 6 it was between 20 and 30 mmHg, in 3 between 30 and 40

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*IL 413 Blood–gas analyser calibrated with known gases.

Table 1 *Clinical details of 20 infants given tolazoline*

Group	*Case*	*Sex*	*Birthweight (g)*	*Gestation (weeks)*	*Diagnosis**	*Outcome*
B	1	M	1360	31	HMD, PIE, PT, S	Survived
A	2	M	2013	33	HMD, PT, C	Survived
B	3	M	1333	28	HMD, PT, IVH	Died
A	4	M	1825	31	HMD, C, RF, PH	Died
A	5	F	1080	27	HMD	Survived
B	6	F	1930	37	Rh, HMD, SAH	Died
B	7	M	1798	33	HMD, S, C, IVH	Died
B	8	M	2430	33	HMD, IVH, SAH	Died
A	9	F	930	26	HMD, PT	Survived
A	10	M	2000	33	HMD	Survived
A	11	M	1750	32	HMD	Survived
B	12	F	700	26	HMD, PT, C, SAH, IVH	Died
A	13	F	890	30	HMD	Survived
A	14	M	2020	35	HMD	Survived
B	15	F	2100	31	HMD, Rh, PT	Survived
A	16	M	1158	32	HMD	Survived
B	17	F	1000	28	HMD, PIE, C, PH, SAH	Died
A	18	M	750	31	HMD, S	Died
A	19	F	1300	30	HMD	Survived
B	20	M	1045	30	HMD, PT, C, SAH, IVH	Died
Mean			1486	30·8		

*HMD = hyaline membrane disease, IVH = intraventricular haemorrhage, PIE = pulmonary interstitial emphysema, RF = renal failure, PT = pneumothorax, Rh = severe rhesus isoimmunisation (see text), S = septicaemia, C = coagulopathy (see text), PH = pulmonary haemorrhage, SAH = subarachnoid haemorrhage.

mmHg, and in the remaining infant the Pa_{O_2} was 66 mmHg. Subsequent doses of tolazoline were given in 11 infants, who responded to the first dose, and in whom hypoxaemia recurred. Chest *x*-rays were taken before the use of tolazoline if time allowed, so as to exclude pneumothorax as a cause for the infant's deterioration. In 7 infants, pancuronium bromide in a dose sufficient to paralyse spontaneous respiration (0·03–0·05 mg/kg repeated as necessary) was given without improvement before the administration of tolazoline.

The dose of tolazoline hydrochloride was 1–2 mg/kg body weight given over 30 seconds, into a scalp vein (10 infants), into another vein (2 infants), or into the umbilical artery (8 infants).

Ventilator settings were recorded before and after each dose of tolazoline. In the 15 infants in whom the abdominal aortic Pa_{O_2} was recorded continuously, the records were analysed to determine the Pa_{O_2} one min before and the peak Pa_{O_2} within 10 min after the administration of tolazoline. In addition blood–gas analysis was performed before and after each dose of tolazoline.

Mean airway pressure (MAP) was calculated for each of the ventilator settings, using the formula

$$\frac{(\text{PAP} \times \text{inspired ratio}) + (\text{EEP} \times \text{expired ratio})}{\text{inspired} + \text{expired ratio}}$$

and changes in Pa_{O_2} were determined from the blood–gas and abdominal aortic oxygen electrode data. MAP has been shown to correlate well with alveolar arterial oxygen difference at slow respiratory rates (Herman and Reynolds, 1973), and so was used to measure changes in ventilation which might have contributed to changes in Pa_{O_2}. Changes in pH, Pa_{CO_2}, and base excess (BE) were also noted.

Blood pressure was measured by ultrasound using a Doppler (1 infant) or by a transducer (Hewlett Packard) attached to the umbilical arterial catheter (12 infants).

Tolazoline administration is followed by peripheral vasodilatation (Grover *et al.*, 1961), and this was apparent in our infants. In 13 of them infusion of either whole blood, normal saline, or 5% sodium bicarbonate was needed after the administration of tolazoline to maintain an adequate circulating blood volume and a normal blood pressure.

The data obtained relating to each dose of tolazoline were analysed, using Student's paired or unpaired *t* test, as appropriate.

Results

Data obtained from continuously recorded abdominal aortic Pa_{O_2} are summarised in Table 2. An example of such a record showing the response to tolazoline from which these data were obtained is shown in the Figure. Data obtained from analysis of samples of arterial blood are summarised in Table 3.*

The 15 infants in which abdominal aortic Pa_{O_2} was continuously recorded received 41 doses of tolazoline (Table 2). There was a highly significant rise of 26 mmHg in the abdominal aortic Pa_{O_2} after tolazoline injection ($P<0{\cdot}001$), while $F_{I_{O_2}}$ and MAP did not change significantly.

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*Complete data may be obtained from the authors on request.

Table 2 *Summary of data obtained from abdominal aortic oxygen electrode*

Group	*Doses*	*Before tolazoline*			*After tolazoline*		
		Mean MAP (cm H_2O)	*Mean F_{IO_2}*	*Mean Pao_2 (mmHg)*	*Mean Δ MAP (cm H_2O)*	*Mean Δ F_{IO_2}*	*Mean Δ Pao_2 (mmHg)*
Response to all doses of tolazoline							
All patients (n = 15)	41	17·0	1·0	28	−0·02 (NS)	0	+26 $(P<0\cdot001)$
Group A (n = 9)	24	16·2	1·0	34	0	0	+38 $(P<0\cdot001)$
Group B (n = 6)	17	18·2	1·0	21	−0·05 (NS)	0	+8 $(P<0\cdot05)$
Response to 1st dose tolazoline only							
All patients (n = 15)	15	18·6	1·0	22	+0·2 (NS)	0	+39 $(P<0\cdot005)$
Group A (n = 9)	9	17·4	1·0	27	0	0	+56 $(P<0\cdot005)$
Group B (n = 6)	6	20·3	1·0	14	+0·4 (NS)	0	+14 $(P<0\cdot01)$

Group A: Infants without intracranial haemorrhage or pneumothorax; Group B: infants with either intracranial haemorrhage (4) or pneumothorax (2).

In the 9 infants who were not shown subsequently to have intracranial haemorrhage or pneumothorax (group A), the mean rise of 39 mmHg in abdominal aortic Pao_2 was significantly greater than in the 6 infants with either intracranial haemorrhage or pneumothorax (group B) in whom the mean rise in abdominal aortic Pao_2 was 8 mmHg $(P<0\cdot01)$. The response to tolazoline was more marked after the first dose, the mean rise in abdominal aortic Pao_2 in all patients being 39 mmHg. In group A the mean rise of 56 mmHg was significantly greater than in group B, in which the mean rise was 14 mmHg $(P<0\cdot01)$.

Blood-gas data were obtained before and after 33 doses of tolazoline in 20 infants (Table 3). There was a significant rise of 21 mmHg in Pao_2 after tolazoline injection $(P<0\cdot01)$ which occurred despite a fall in F_{IO_2}, while MAP did not change significantly. No significant change in pH, Paco_2, or base excess occurred. In the 11 infants who were not shown subsequently to have intracranial haemorrhage or pneumothorax (group A), the mean rise in Pao_2 was 26 mmHg compared with the mean rise in Pao_2 of 10 mmHg in the 9 infants with intracranial haemorrhage or pneumothorax (group B). This difference is not statistically significant. If the 2 patients with pneumothorax are excluded from group B, the mean rise in Pao_2 for the group is 4 mmHg which is significantly different from the rise in group A $(P<0\cdot05)$. When only the response to the first dose of tolazoline is considered, the mean rise in Pao_2 after tolazoline was 33 mmHg $(P<0\cdot01)$ which occurred despite of a fall in F_{IO_2}, while MAP did not change significantly. In group A the mean rise in Pao_2 of 49 mmHg was significantly greater than in group B in which the mean rise was 14 mmHg $(P<0\cdot05)$.

Discussion

Tolazoline hydrochloride is chemically related to the sympathomimetic amines and histamine. It is a short-acting alpha adrenergic blocking agent, but in the doses used in the clinical situation this effect is negligible. It is also a histaminic agent and has a direct nonadrenergic relaxant action upon vascular smooth muscle, the vasodilator effect being greatest in regions where vasoconstriction is most pronounced (Grover *et al.*, 1961). Tolazoline has been shown to relieve pulmonary vasoconstriction and in this respect it is believed to be most effective in those cases where pulmonary vascular resistance is increased due to a generalised constriction of hypertrophied small muscular arteries (Grover *et al.*, 1961). This situation is similar to that seen in severe hyaline membrane disease with hypoxaemia, and pulmonary vasospasm has been demonstrated in such infants by Chu *et al.* (1967). The possible value of tolazoline in the management of severe hypoxaemia in infants with hyaline membrane disease has been suggested (Goetzman *et al.*, 1976).

In our 20 deteriorating infants we demonstrated a significant rise in arterial Pao_2 in response to tolazoline. The babies acted as their own controls as the drug was given only as a last resort when all other treatments had failed and it was felt that death was imminent. In infants who did not have intracranial haemorrhage or pneumothorax as a cause for their severe refractory hypoxaemia the improvement was more pronounced. The difference in response to tolazoline between the two groups was more marked with the first dose than with subsequent ones.

Of the 10 infants who had an obvious clinical

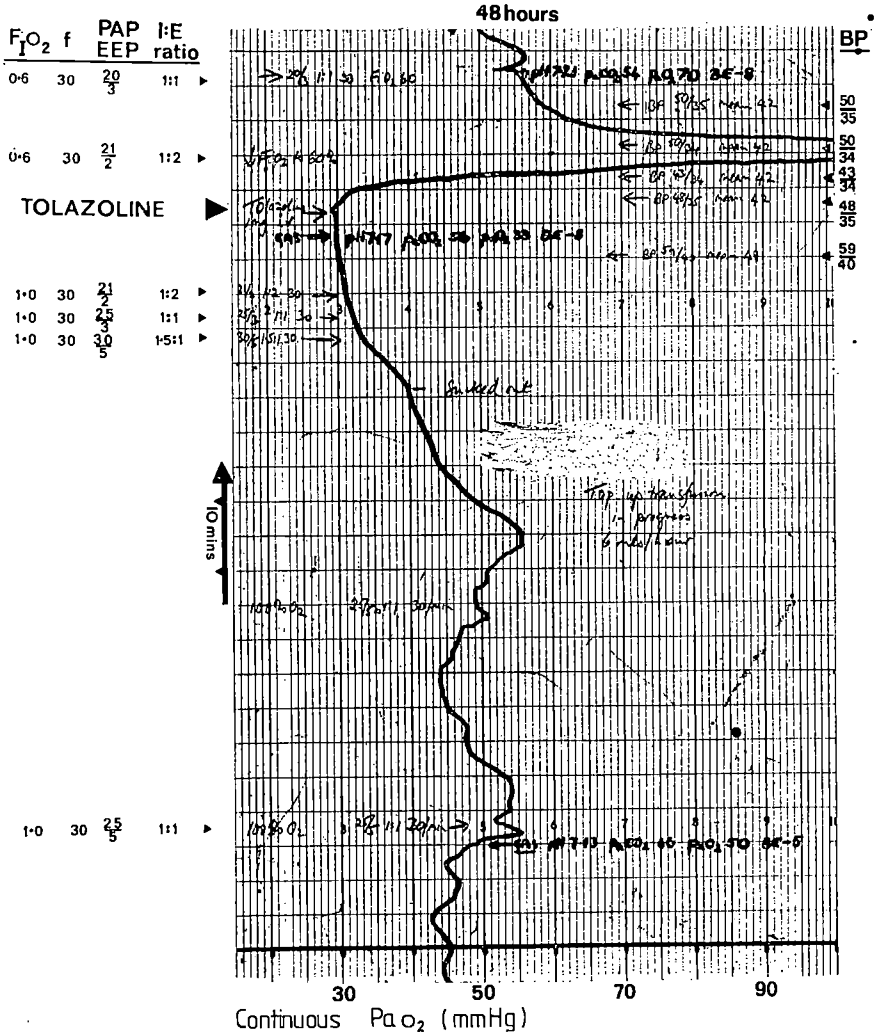

Figure *Continuous Pao_2 trace from baby in group A given intravenous tolazoline. Read trace from below up. Abbreviations as in text.*

response to tolazoline, 9 survived, whereas only 2 out of 10 who failed to respond survived; both of these infants were subsequently shown to have pneumothoraces which were satisfactorily drained. These results suggest that the improvement in oxygenation resulting from the administration of tolazoline may lead to better survival in a group of infants who would otherwise have a high mortality. It is suggested that the mechanism for improvement is the breaking of the progressive vicious circle of increasing hypoxaemia, acidosis, and pulmonary vasoconstriction.

The known potential side effects of tolazoline are related to systemic hypotension and histaminic effects on the gastrointestinal tract. In our series systemic hypotension was not a significant problem because care was taken to maintain the circulating blood pressure. However, we consider that monitoring blood pressure is essential if this drug is used. Renal failure was observed in one patient, who died. This could be attributed in part to tolazoline, but the failure may have been due to hypoxic damage caused before the use of tolazoline. Extreme irritability accompanied by bloodstained cerebrospinal fluid observed in 2 patients, both of whom survived, might have resulted from leakage of red

Table 3 *Summary of data obtained from blood–gas analysis*

	Doses	*Before tolazoline*							*After tolazoline*						
		Mean MAP (cmH_2O)	*Mean f*	*Mean F_IO_2*	*Mean PaO_2 (mmHg)*	*Mean pH*	*Mean $PaCO_2$ (mmHg)*	*Mean BE*	*Mean ΔMAP (cmH_2O)*	*Mean Δf*	*Mean ΔF_IO_2*	*Mean ΔPaO_2 (mmHg)*	*Mean ΔpH*	*Mean $\Delta PaCO_2$ (mmHg)*	*Mean ΔBE*
Response to all doses of tolazoline															
All patients (n = 20)	33	16·5	32	1·0	33	7·02	69	−11	−1·0 (NS)	+3·0 ($P<0·05$)	−0·06 ($P<0·05$)	+21 ($P<0·01$)	0·01 (NS)	−3·3 (NS)	−1·0 (NS)
Group A (n = 11)	19	15·8	30	1·0	38	7·13	55	−9	0·4 (NS)	+2·4 ($P<0·05$)	−0·09 ($P<0·05$)	+29 ($P<0·01$)	0·01 (NS)	−3·7 (NS)	−1·2 (NS)
Group B (n = 9)	14	17·6	33	0·98	26	6·95	89	−12	−1·7 (NS)	+3·9 (NS)	−0·02 (NS)	+9 (NS)	0·01 (NS)	−2·9 (NS)	−0·8 (NS)
Response to 1st dose of tolazoline only															
All patients (n = 20)	20	17·6	30	1·0	27	7·03	75	−10	−2·0 (NS)	+4·0 ($P<0·01$)	−0·09 ($P<0·05$)	+33 ($P<0·01$)	0·01 (NS)	−7·2 (NS)	−2·2 (NS)
Group A (n = 11)	11	16·4	29	1·0	29	7·11	61	−9	−1·3 (NS)	+3·6 ($P<0·05$)	−0·14 ($P<0·05$)	+45 ($P<0·01$)	0·01 (NS)	−8·4 (NS)	−2·5 (NS)
Group B (n = 9)	9	19·0	32	1·0	23	6·94	92	−13	−2·9 (NS)	+4·4 (NS)	−0·03 (NS)	+19 (NS)	0·02 (NS)	−5·8 (NS)	−1·8 (NS)

Group A: infants without intracranial haemorrhage or pneumothorax; Group B: infants with either intracranial haemorrhage (4) or pneumothorax (6).

cells through a distended cerebral capillary bed to the cerebrospinal fluid. In neither case presenting in this manner was there apparent abnormality in the coagulation status which has been associated with subarachnoid haemorrhage (Chessells and Wigglesworth, 1971). Gastrointestinal problems were not encountered, although a potential hazard from reduced splanchnic flow might be necrotising enterocolitis; abdominal distension and haemorrhage have been well described by Goetzman *et al.* (1976).

We agree with Levin *et al.* (1976) that one definite indication for tolazoline is hypoxaemia with demonstrable difference between upper and lower body Pao_2, implying persistence of transitional right-to-left circulation through the ductus arteriosus. This, in fact, occurred in only one baby in our series.

We conclude that there is a place for the use of tolazoline in a severely hypoxaemic infant with hyaline membrane disease who is being ventilated with an inspired oxygen concentration of 100% and in whom the Pao_2 is unresponsive to alteration of ventilator settings. In these cases where chest movement is clinically normal and where pneumothorax has been radiologically excluded, tolazoline may have a dramatic effect.

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Factors affecting neonatal jaundice

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SUMMARY Plasma bilirubin was estimated on 690 term infants on about the 6th day of life. Perinatal factors were recorded and the results analysed. Hyperbilirubinaemia was defined as a level >205 μmol/l (12 mg/100 ml) and this was present in 20% of cases. Three factors—epidural analgesia, breast feeding, and poor weight recovery—showed highly significant associations with jaundice. The relative importance of these is discussed and compared with recent reports. Induction of labour, for reasons other than postmaturity, and a gestational age <39 weeks showed a slightly increased incidence of jaundice. There was no correlation with other factors tested including oxytocic drug administration. Despite the high incidence (20%) of hyperbilirubinaemia, only 2.5% infants needed treatment and none required exchange transfusion. Radical changes in obstetric management or infant feeding are not indicated.

Since the claim by Mast *et al.* (1971) and Quakernack and Mast (1971) that oxytocic drugs were related to an increased incidence of neonatal jaundice, reports on this and on other maternal or perinatal factors have shown conflicting results (Ghosh and Hudson, 1972; Davidson *et al.*, 1973; Eden *et al.*, 1974; Gould *et al.*, 1974; Chalmers *et al.*, 1975). It was therefore decided to carry out a prospective study at the Birmingham Maternity Hospital taking into account the recent changes in obstetric and paediatric practice to assess incidence, related factors, and clinical implications.

Method

Two representative lying-in wards at the hospital were chosen. 903 mothers were delivered of liveborn infants between September 1974 and July 1975 inclusive, but 180 of these babies were discharged before 6 days and a further 33 were preterm, of low birthweight, Coombs-positive, or delivered by ventouse, and so were excluded. The 180 infants were compared with the remaining 690 and no significant differences were found regarding ethnic group, social class, gestation, or birthweight. There were however rather fewer vertex deliveries and rather more forceps and caesarean births among the infants who stayed the full 6 days. Otherwise the 690 infants studied were representative of term babies delivered at that time in the hospital.

The maternal history, birth details, and infants' data were recorded on a proforma suitable for computer analysis.

Assessment of jaundice. As the plasma bilirubin (PB) level rises and then falls in the normal newborn during the first week, the timing of the samples needs to be as constant as possible to give comparable results. Sampling was therefore arranged to coincide with the metabolic screening test on about the 6th day. Those infants showing clinical jaundice had PB levels measured earlier and 17 infants with PB levels >308 μmol/l (18 mg/100 ml) before the 6th day received phototherapy. In these the highest recorded levels were used in the analysis. PB was measured by a modification of the method of White *et al.* (1958).

Despite a general alertness for jaundice, surprisingly high PB levels were obtained for the first time at the routine 6th day heel prick in some babies. 32 (4·4%) had PB levels >205 μmol/l (12 mg/100 ml) and 9 (1·2%) >256 μmol/l (15 mg/100 ml). These might have been missed, emphasising the need for all infants to have blood samples taken if the true incidence of hyperbilirubinaemia is to be obtained.

Results

A distribution curve for the whole series was plotted

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within 34 μmol/l (2 mg/100 ml) groups (Figure). The interplay of the various factors and the levels of PB were repeatedly analysed on the computer. It was found that a level of 205 μmol/l (12 mg/100 ml) and above showed the most significance, and this was defined as hyperbilirubinaemia. Mean PB levels were also recorded for comparison.

The following factors showed no effect on jaundice: ethnic group, ABO blood group, maternal age, time of year, type of delivery, birthweight, birth rank, vitamin K administration, sex, maternal toxaemia, and social class.

The gestational age of all these infants was >37 weeks and there was a slight increase both of mean PB levels and of hyperbilirubinaemia in those <39 weeks (Table 1). The mean gestational age was taken into account in each subsequent analysis and it showed a similar distribution throughout the different clinical groups.

Six clinical groups remained to be analysed further: previous contraceptive pill taking by the mother, oxytocic drug, labour onset, epidural analgesia, method of feeding, and weight recovery.

Table 2 shows how these clinical groups compared in respect of mean PB levels and percentage of babies with hyperbilirubinaemia. There was no difference in respect of pill taking or oxytocic administration. When induction of labour was analysed for the whole group there was no apparent effect but when the cases were divided into those induced for prolonged pregnancy and those induced for other reasons there were significant differences.

Epidural analgesia, weight recovery, and breast or artificial feeding all gave highly significant differences in respect of percentage jaundice and, the last two, in respect of mean PB levels as well. The clinical groups were therefore analysed a further three ways according to whether the mothers had received epidural analgesia or not, whether the baby regained birthweight above or below 95%, and whether it was wholly breast or artificially fed. Epidural analgesia and weight recovery did not alter the results in Table 2, but taking the 590 wholly breast-fed or wholly bottle-fed babies there were some minor changes. The mean PB level of the breast fed 'pill' group was significantly higher than the 'no pill' but the difference in hyperbilirubinaemia was not. Oxytocic drug and labour onset remained virtually the same. The interrelationships between the three

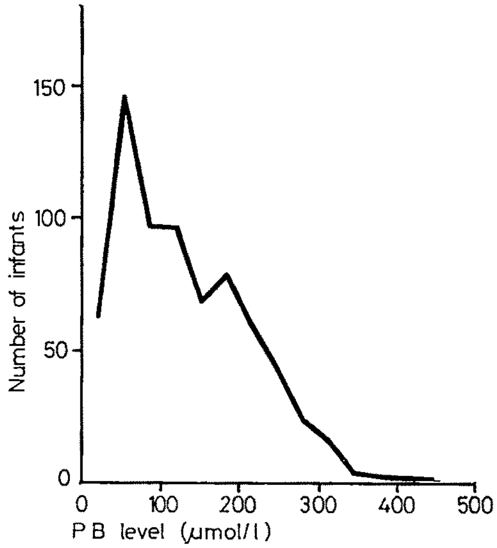

Figure *Frequency distribution of plasma bilirubin levels for 690 infants.*

Table 1 *Jaundice and gestation*

Gestation	*n*	*Mean PB* (μmol/l)	*Hyperbilirubinaemia* (%)
<39 weeks	99	159	27·3
		***	
39 to 40 weeks	164	130	18·3
40 to 41 weeks	242	120	18·2
41 weeks and over	125	121	17·6

*** P<0·001.
Conversion: SI to traditional units—1 μmol/l ≈ 0·06 mg/100 ml.

Table 2 *6 clinical groups and the incidence of jaundice*

Group	*n*	*Mean PB* (μmol/l)	*Hyperbilirubinaemia* (%)
All cases	690	130	20·0
Pill			
No	274	123	18·7
Yes	390	135	21·0
Oxytocic drugs			
No	407	133	22·1
Yes augmented	117	127	21·4
Yes induced	290	135	22·4
Labour onset			
Spontaneous	330	125	19·1
Induced, prolonged pregnancy	82	* 111	14·6
		**	*
Induced, other	224	143	24·6
Epidural			
No	178	122	11·8
			***
Yes	512	133	22·9
Weight recovery			
≥95%	411	119	14·6
		***	***
<95%	165	162	33·3
Feeding			
Artificial	268	109	12·3
		***	***
Breast	312	***144	* 25·3
Mixed	110	138	23·6

*P<0·05; **P<0·01; ***P<0·001.
Conversion as in footnote to Table 1.

significant factors is further examined in Table 3. The effect of epidural analgesia on hyperbilirubinaemia was reduced in significance and this was more apparent in the breast-fed than the artificially-fed group, probably because the size of the sample was smaller. Poor weight recovery did not show an effect in the artificially-fed infants so it was concluded that breast feeding itself rather than any concomitant underfeeding was the more important factor.

Discussion

An increasing incidence of neonatal jaundice has been reported by several authors (Campbell *et al.*, 1975; Sims and Neligan, 1975; Smith and Wilson, 1978), while in Birmingham the incidence of hyperbilirubinaemia (>205 μmol/l) has apparently risen from 5·6% (Wood *et al.*, 1962) to 20% in 1975. These figures are not strictly comparable however because in the early years routine blood tests were not done and, as already shown, 4% of babies with significant levels might have been omitted. Despite this, and a recent questionnaire to the contrary (Friedman *et al.*, 1977), it appears that in many centres there has been a real increase, although this may have levelled off since 1972 (Friedman *et al.*, 1978).

The incidence of hyperbilirubinaemia reported from different centres ranged from about 5% in Belfast (McConnell *et al.*, 1973), 8% in Liverpool (Beazley and Alderman, 1975), 9% in Cardiff (Davies *et al.*, 1973), 10% in Edinburgh (Chew and Swann, 1977), 12% in London (Campbell *et al.*, 1975), and 21% in Oxford (Calder *et al.*, 1974), which alone closely approached our own figure of 20%.

The pill and breast feeding. Since the report of Wong and Wood (1971) of a higher incidence of jaundice in breast-fed babies of mothers who had previously taken the pill, the oestrogen content has been much reduced and this may be the explanation (Wong, 1974) for a difference (P < 0·05) being seen only in mean PB levels and not in hyperbilirubinaemia in the present series.

Table 3 *Epidural analgesia and weight recovery in breast- and artificially-fed babies*

Group	*n*	*Mean PB (μmol/l)*			*Hyperbilirubinaemia (%)*		
		Breast fed		*Artificially fed*	*Breast fed*		*Artificially fed*
All cases	580	144	†††	109	25·3	†††	12·3
Epidural							
No	152	140	††	98	16·9 *	†	5·3 **
Yes	428	146	†††	114	28·1	†††	15·0
Weight recovery							
>95%	349	132 ***	††	104	20·7 **	††	10·3
<95%	129	174	†	127	39·0	†	17·2

*Vertical differences between clinical groups; †horizontal differences between type of feeding.
*†P<0·05; **††P<0·01; ***†††P<0·001.
Conversion as in footnote to Table 1.

Oxytocic drugs. The dose of oxytocin in this series was low (< 10 units for most labours) which supports the view of Davies *et al.* (1973) and Beazley and Alderman (1975) that the effect, if any, is likely to be dose related. Our results showed no increase in either mean PB levels or of hyperbilirubinaemia whether the oxytocin was given to induce or augment labour.

Labour onset. Only when induction was divided according to its two main indications—prolonged pregnancy, on the one hand, or for obstetric or medical reasons, on the other, was there any difference. Any pronounced increase of preterm induction as a result of individual hospital policy would be liable to increase the jaundice risk, as shown in Table 1. This accords with the findings of Calder *et al.* (1974) and Sims and Neligan (1975) where the concept of enzyme priming in spontaneous labour was raised.

Epidural analgesia. Davies *et al.* (1973), Campbell *et al.* (1975), Sims and Neligan (1975), and Friedman *et al.* (1978) question the use of bupivacaine as a cause of hyperbilirubinaemia, and this study showed a highly significant difference. Whether this was due to the analgesic drug itself or to a related factor is uncertain. It is unlikely to be due to any post-delivery drug administered to the mother and secreted in her milk as it was also shown in the artificially-fed babies. Sims and Neligan (1975) thought that the association of epidural with jaundice in their series was probably because of the need for efficient pain relief during high dose oxytocin infusion after deliberate induction of labour. If this was the explanation in our epidural cases, one would expect that the proportion of deliberately induced babies would be significantly higher in those with hyperbilirubinaemia than in the rest. In fact the percentages were 43 and 38% respectively, showing no significant difference. The forceps rate in epidurals was as expected higher (52·5%) compared with nonepidurals (9%). However the incidence of hyperbilirubinaemia in the epidurals was the same whether they were delivered by vertex (22·6% hyperbilirubinaemia) or by forceps (21·6% hyperbilirubinaemia), again suggesting that the epidural is the relevant factor.

Feeding and weight recovery. From Table 3 it appears that breast feeding is more relevant than poor weight

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gain. In Newcastle, Sims and Neligan (1975) also noted such a relationship and felt that it could not be explained by the jaundice causing the weight loss as the lowest weight was usually recorded on the 3rd day while the peak bilirubin level was not reached before the 4th or 5th day. This suggests that some human milk may contain an icterogenic factor but this may not necessarily be an endogenous one.

Other factors. In a comprehensive analysis of some 20 different drugs administered to the mother in labour, Drew and Kitchen (1976) showed that aspirin, barbiturate, and some others lowered the newborn baby's PB level on the 2nd and 3rd days while diazepam and oxytocic drugs raised it. The effect was small and probably only of significance in the at risk infant. It would be interesting to extend that kind of investigation in both breast-fed and artificially-fed infants during the first week of life.

In conclusion it appears that the high incidence of jaundice in this series was probably associated with the frequency of epidural analgesia (74%) and of wholly breast-fed babies (45%). As stated the only other report of a similar incidence of hyperbilirubinaemia was from Oxford (Calder *et al.*, 1974) where 85% of mothers had epidurals and 29% wholly breast fed their infants.

These factors overshadowed the others so that previous pill taking by the mother and oxytocic administration in the relatively low dosage used had no effect. Induction of labour showed its expected effect only if cases induced for postmaturity were excluded.

The question remains as to whether the bupivaine and the breast milk themselves are icterogenic or whether the women concerned received different analgesic or hypnotic drugs from the others and these might be the active agents.

While obvious jaundice in her infant can cause maternal anxiety and may delay discharge from hospital it should be noted that only 17 (2·5%) of the 690 infants had PB levels >308 μmol/l (18 mg/100 ml) at which phototherapy or feed change was instituted. None reached 427 μmol/l (25 mg/100 ml) which was the agreed level for exchange transfusion. Evidence for long-term handicap after nonhaemolytic jaundice of this degree is tenuous. The findings by Boggs *et al.* (1967) and later by Scheidt *et al.* (1977) of delayed psychomotor development at 8 months and one year in infants with neonatal PB levels of about 256 μmol/l made inadequate allowance for gestational age at birth and later reports on these children are still awaited. 17 of 18 children found to be deaf by Fenwick (1975) after similar PB levels had haemolytic disease and, in the 18th, the child's mother had an obscure jaundice. In an earlier series of 371 jaundiced infants reported by us (Culley *et al.*, 1970), full neurological and psychomotor examination at age 5 years showed no ill effects unless PB exceeded 342 μmol/l (20 mg/100 ml).

There is therefore no reason for doctors to reduce their advocacy of breast feeding or to make radical changes in the management of labour until the responsible factors have been more clearly identified.

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Childhood asthma. A controlled trial of family psychotherapy

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SUMMARY In an attempt to evaluate the effectiveness of family psychotherapy as an adjunct to conventional treatment in childhood asthma, children with moderate to severe asthma were randomly allocated to a control group or to an experimental group; the latter group received 6 hours of family treatment during a 4-month period, and both groups had standard medical treatment. While there was no significant difference between the two groups on three parameters, the experimental group were significantly better in day-wheeze score and thoracic gas volume. These results suggest that family treatment in selected cases may have a place in the overall management of childhood asthma, and that more research with larger numbers of children is necessary.

While it is accepted that the basic abnormality in childhood asthma is the combination of bronchial lability and atopic status (König and Godfrey, 1973), it is well known that emotional factors play an important part in its aggravation and maintenance (Purcell *et al.*, 1969; Graham and Rutter, 1970; Godfrey and Silverman, 1973; Pilling, 1975; Williams, 1975). McNichol and his colleagues stated that 'patients with severe ventilatory disturbance should be assessed psychologically and the family interrelationships assessed' (McNicol *et al.*, 1973). The implication of this is that psychological methods of treatment as an adjunct to medication may be indicated either for the asthmatic child or his family.

Despite the many reports on emotional aspects of childhood asthma, there have been very few controlled studies of psychological methods of treatment. Some modest claims have been made for the effectiveness of such behavioural methods of treatment as conditioning and relaxation (Lukeman, 1975; Kotses *et al.*, 1978), while Pinkerton (1967) showed that a group of 13 asthmatic children treated with short-term individual psychotherapy had a lower relapse rate than did a matched control group of 12 children. More recently spectacular success was claimed for the use of family psychotherapy in the treatment of intractable childhood asthma (Liebman *et al.*, 1974). The validity of this claim is diminished by the absence of a control group.

However on the basis that 'it is at home with persons who are most loved (or at times hated) that emotional relationships are most intense, and most likely to produce symptoms' (Apley and Mac Keith, 1968), we decided to test the effectiveness of family psychotherapy as an adjunct to standard medical management of childhood asthma. No controlled studies have been published on family psychotherapy for any childhood conditions.

Methods

The children were attending the asthma clinic at a postgraduate teaching hospital, where many patients are referred for a 2nd, or even a 3rd, opinion. Any child between the ages of 4 and 14 with grade C or D asthma (as defined by McNicol and Williams, 1973) was considered eligible for the study.* Their families were then randomly allocated to the experimental (group A) or control group (group B). Three of the families had more than one asthmatic child, and so all were included in the assessments. Initially, group A comprised 17 families with 21 asthmatic children, and group B comprised 16 families with 16 asthmatic children. The two groups were homogeneous with respect to severity of asthma, age (range 4–14), social class, and psychological health. There were more boys than girls in group A, but as the natural history of asthma does not vary between the sexes

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**Grade C* children with a continuing history of episodic asthma over a number of years.
Grade D children with a current history of very frequent or chronic unremitting asthma.

(McNicol *et al.*, 1973), this was not considered to matter.

In group A 10 children were using cromoglycate (Intal) or beclomethasone (Becotide) regularly, and 8 were using only bronchodilators. In group B 6 children were using cromoglycate or beclomethasone regularly, and 5 were using only bronchodilators. Two children in group A and one in group B had received intermittent courses of corticosteroids before the trial but not during it.

Each child was assessed using diary cards, recording day-wheeze and activity limitation on a 0–3 scale of ascending severity, and the peak expiratory flow rate (PEFR) was measured before giving the morning or evening medication. These measurements were made during a 6-week baseline period before the start of treatment, and were repeated during a similar 6-week follow-up period one year later. One measurement of forced expiratory volume ($FEV_{0\cdot75}$) and thoracic gas volume (TGV) was made during each period. In addition, the children and families were fully assessed psychologically before treatment began, and the families classified according to Schneidermann—as emotionally healthy, moderately disturbed, or poorly adjusted (Schneidermann *et al.*, 1976).

Children in group B were seen and appropriately treated by the paediatrician at 3-weekly intervals during a 4-month period. Drug regimens were monitored and changed if necessary, and general management of the asthma was discussed, but there was no specific attempt to clarify or alter family relationships. Children in group A were seen by the paediatrician in the same way but these children also attended with their families on the same day for 6 one-hour sessions of family psychotherapy. Details of this treatment are to be found elsewhere (Lask, 1979; Lask and Kirk, 1979) but a brief summary is given below.

Family psychotherapy. This has as its conceptual focus the whole family system with particular emphasis on understanding the individual's symptoms and behaviour as arising from and feeding back into the general family system of interaction. The family therapist would meet the *whole* family together and, in the case of an asthmatic child, would focus on such themes as the varying attitudes to the illness, the doctor and the medication, the fear of death, and the experiencing of painful and frightening emotions. By dealing with such themes and helping to adjust attitudes away from the extreme and towards the more realistic, he would work towards an improvement in the psychological wellbeing of the family. In this way there would be an alleviation of some of the stresses which, in interaction with other physical factors, contribute to the recurrence of asthmatic attacks (Pinkerton, 1967).

Results

Some children who were initially assessed were not included in the follow-up. One family in group B dropped out after the initial assessment, and one family in each group dropped out after the first session. A further 3 children in group B were excluded from follow-up as one of them had failed to attend most of the appointments while two others were sent to special boarding-schools for asthmatic children because their health had so deteriorated. Finally, 3 children in group B, were unable to cooperate in the measurement of TGV. Consequently, at final follow-up there were 18 children in group A and 11 in group B of whom 3 had each missed one test.

The peak flow was expressed as percentage predicted normal for height, and the mean morning and evening peak flows for the two 6-week assessment periods were determined (Table 1). There was no significant difference between the two groups, but there was a significant improvement between baseline and follow-up scores in group A, but not in group B ($P<0\cdot005$, paired *t* test).

The $FEV_{0\cdot75}$ and the TGV were expressed as percentage predicted normal for height (Table 1). There was no significant change in $FEV_{0\cdot75}$. TGV is an index of lung overinflation and therefore if this falls there has been an improvement. There was a significant improvement in TGV in group A compared with group B ($P<0\cdot02$, rank sum test).

The activity and day-wheeze scores were expressed as the total score for each 6-week baseline and follow-up period (Table 2). There was no significant difference in change of activity score, but the day-wheeze score improved in favour of the experimental group ($P<0\cdot01$, rank sum test).

The results of the respiratory function tests and the symptom scores expressed as the differences

Table 1 *Respiratory function, mean values for experimental and control groups expressed in percent predicted for height*

Group	*PEFR*				*$FEV_{0\cdot75}$*		*TGV*	
	a.m.		*p.m.*					
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Experimental								
Baseline	53	21	61	20	71	15	155	45
Follow-up	66	20	72	15	70	14	146	38
Control								
Baseline	49	22	54	20	67	18	158	31
Follow-up	56	22	60	22	62	18	176	33

Table 2 *Symptom scores, mean values for experimental and control groups*

Group	*Day-wheeze*		*Activity*	
	Mean	*SD*	*Mean*	*SD*
Experimental				
Baseline	14	15	13	13
Follow-up	7	8	5	8
Control				
Baseline	20	12	20	12
Follow-up	21	11	15	13

between baseline and follow-up values are shown in the Figure.

Discussion and conclusions

Although the number of children in this study was small, we believe that the findings warrant a more detailed evaluation of such treatment. That there should be a significant improvement in an objective test of respiratory function is in accordance with the conclusions of Pinkerton (1967) that many studies seem to indicate that psychodynamic factors are contributing to most cases of childhood asthma, and in turn will affect ventilatory function. We believe that the family treatment has helped to alleviate psychopathology within the family, and thus has contributed to an alleviation of the asthma. As we know of no other controlled studies showing improved respiratory function in asthmatic subjects after psychotherapy, and family therapy itself has been the subject of very few controlled studies, this approach should be more fully evaluated. Further studies should be on a much larger number of children, and, if possible, allowance should be made for the effect of increased attention. It should be added that the time allotted to the family psychotherapy was relatively short. Liebman *et al.* (1974) treated such families once a week for 1½ hours at a time for a one-year period. We recommend a compromise between the two. We suggest that family therapy may have a part to play in selected cases of childhood asthma, and especially in those cases where the asthma is not being well controlled with conventional treatment methods.

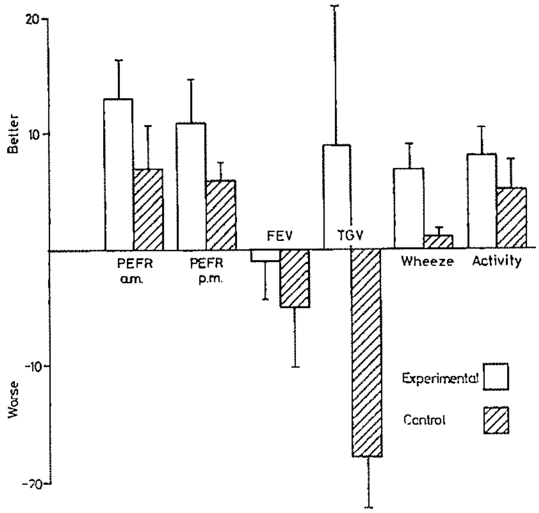

Figure *Differences (and SEM) between the baseline and follow-up values as shown in Tables 1 and 2.*

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Antigen-antibody complexes in the serum of patients with juvenile chronic arthritis

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SUMMARY IgG-containing antigen-antibody complexes were detected in the sera of all of 7 patients with the systemic form of juvenile chronic arthritis, usually at high levels. Only 9 of 25 patients with the polyarticular form had such complexes, usually at low levels. Three patients had low levels of serum IgA which were probably drug induced; the one patient with low C2 and the 3 with low yeast opsonisation were probably not more than to be expected in a random population.

The aetiology and pathogenesis of juvenile chronic arthritis (JCA) remains unknown, but it has a number of features in common with chronic antigen-antibody complex disease—especially the joint, eye, and skin manifestations. Deposition of immunoglobulin and complement in the joints (Munthe and Natvig, 1972) is consistent with this, but we know of only one report of tests for presumed antigen-antibody complexes (aac) in the blood of patients with JCA (Rossen *et al.*, 1977) and they were confined to those with the systemic form of the disease. We therefore report our results of IgG containing aac in patients with systemic and polyarticular JCA.

It has been suggested that persistent circulation of aac results from defects of the clearance functions —antibody, complement, and phagocytes (Soothill and Steward, 1971), and immunodeficiency, especially of IgA, is associated with a range of immunopathological diseases (Amman and Hong, 1971; Soothill, 1976). IgA deficiency is found in a significant minority of JCA patients, apparently as a primary defect (Cassidy *et al.*, 1977; Barkley *et al.*, 1978). Low levels of the second component of complement (C2), interpreted as indicating heterozygosity for the deficiency, have also been reported in association with JCA (Glass *et al.*, 1976). Other complement components are usually normal although some variation occurs during active disease (Bianco *et al.*, 1971). A common defect, apparently of the alternative pathway of complement, detected by defective opsonisation for yeast phagocytosis, is associated with a similar range of diseases as is IgA deficiency (Miller *et al.*, 1968; Soothill and Harvey, 1976, 1977). We have therefore measured, in addition to circulating aac, total haemolytic complement, C2, C3, and C4, IgA, IgG, and IgM, and the opsonisation of yeast for phagocytosis by normal polymorphonuclear leucocytes, in the JCA patients.

Materials

42 patients suffering from JCA (for diagnostic and classification criteria see Ansell and Wood, 1976), age range 6 to 15 years, were studied. 30 had polyarticular disease—23 seronegative and 7 seropositive; 7 had acute systemic disease (they were younger than the rest—age range 4 to 11 years), and 5 had amyloidosis complicating seronegative systemic disease. All were established patients receiving various forms of treatment. Sera from 19 children (age range 2 to 13 years) in hospital for non-immunological disease (largely cold surgery) were also studied.

Methods

Antigen-antibody complexes were measured by the method of Levinsky and Soothill (1977). EDTA was added to serum separated within 3 hours of blood collection, and the released C1q was removed by reaction with insolublised IgG. The serum was then added to a low affinity rabbit IgM antihuman IgG reagent, and the residual capacity of the latter to

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agglutinate IgG coated latex, was measured by counting unagglutinated particles on a Coulter counter. Total complement was measured using an autoanalyser haemolytic method (modified from Nydegger *et al.*, 1972). It was also adapted for measuring C2, using mixtures of a C2-deficient serum (ED), and the test sample. Results were expressed as % of standard. IgG, IgA, IgM, and C3 were measured by a modification of the radial diffusion method of Fahey and McKelvey (1965). Yeast opsonisation was measured by the method of Soothill and Harvey (1976). Results were expressed as opsonisation index (yeasts per polymorph).

Results

The Figure shows the levels of aac in the sera of patients and controls. The maximum inhibition of agglutination by the latter was 20%, which is consistent with the published upper limit of normal (Levinsky and Soothill, 1977). 10 of the 23 patients with seronegative polyarticular disease had raised levels; in only 3 was the value greater than 30%. All 7 patients with systemic disease had raised levels of aac which were considerably higher than those with polyarticular disease. None of the patients with seropositive disease or amyloidosis had raised levels.

Immunoglobulin and complement were measured in 30 patients with polyarticular disease, positive or negative for rheumatoid factor. IgG, IgM, C3, and haemolytic complement values were either normal or high compared with the age-related normal ranges used in the department. This is consistent with previous reports in JCA. IgA was low in 3 patients, all of whom were receiving drugs which could have explained it, and yeast opsonisation was low (<2·5 Y/P) in 3 (2·30, 2·10, and 1·60); all these 6 had polyarticular seronegative disease.

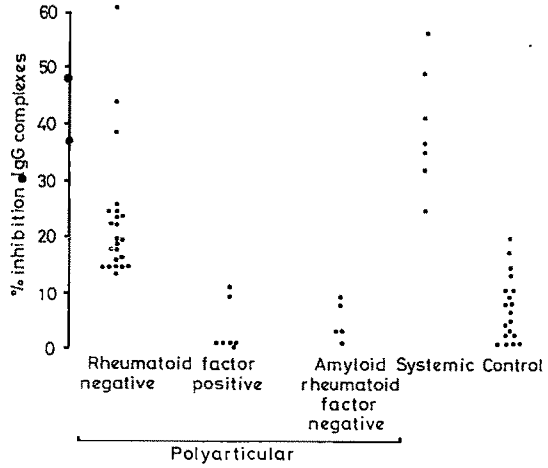

Figure. *Levels of IgG-containing antigen-antibody complexes in children with polyarticular and systemic juvenile chronic polyarthritis expressed as percentage inhibition of agglutination of IgG coated latex by rabbit IgM antihuman IgG reagent.*

Discussion

The high levels of IgG-containing aac in the serum of patients with the systemic form of JCA is consistent with the previous report (Rossen *et al.*, 1977), and with the hypothesis that they may play a part in the pathogenesis of this disease. In contrast, fewer than half of the patients with the seronegative polyarticular form of JCA had raised levels of aac and they had relatively low levels. This casts doubt on their pathogenetic role for this disease but, as the patients were studied at different stages of the disease, and on different treatments, these data do not refute that hypothesis. Antiglobulin antibodies (rheumatoid factor, and others) are low affinity antibodies to human IgG. Since these will agglutinate latex particles, they could produce false-negative results in our test and this could explain the apparent normal levels of aac in the children with positive rheumatoid factor JCA, but the decomplementing step, which entails removal of C1q with an insolublised IgG immunoabsorbate, would also remove rheumatoid factor, and so would lessen this effect. It is also possible, though, that this step might remove rheumatoid factor containing complexes. The negative finding in JCA with amyloidosis is an interesting new observation. Our data suggest that if the aac detected by this technique play a part in the pathogenesis of this disease, it is largely in the systemic manifestations.

Relatively low levels of serum IgA were detected in only 3 patients, and each had received drugs, such as penicillamine, which may have caused secondary IgA deficiency, so none of these patients is certainly among the minority of JCA with primary IgA deficiency (Cassidy *et al.*, 1973, 1977; Barkley *et al.*, 1978). The defect of yeast opsonisation is associated with a number of diseases which are also associated with IgA deficiency, so we measured it in these patients. The frequency (10%) of values below our diagnostic threshold (2·5) is not significantly greater than that of a healthy population (5%—Soothill and Harvey, 1976). Only one had a level of C2 which suggested heterozygosity for C2 deficiency; this is consistent with the reported incidence of such levels in the population and lower than in a previous report in JCA (Glass *et al.*, 1976). Our findings do not suggest that these deficiencies contribute importantly to the aetiology of JCA in our patients, and we could not investigate the relationship of the different possible immunodeficiencies to the aac findings. We can only assume that our patients are different from those studied by Glass *et al.* (1976), and the role of other immunodeficiencies requires further study.

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Reduction of insulin dose on changing diabetic children from standard to monocomponent insulins

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SUMMARY 21 diabetic children requiring >50 units of standard insulin daily were changed to a monocomponent insulin. During the 3 months before the change the insulin dose had risen significantly from a mean of 70 to a mean of 77 units daily. During the 3 months after the change the dose fell significantly to a mean of 53 units daily. This decrease in insulin requirement was associated with a general improvement in diabetic control. This was assessed clinically and measured in 10 children by an analysis of home urine tests and in 8 children by an analysis of 24-hour urine glucose excretion.

There have been significant advances in the manufacture of insulin. This has resulted in solutions that are free from proinsulin, insulin fragments, and other pancreatic contaminants (Schlichtkrull *et al.*, 1972). Such insulins are variously described as proinsulin-free, single peak, or monocomponent insulins, depending on their degree of purity (Root *et al.*, 1972).

The only clear advantage of these insulins is the avoidance or reversal of lipo-atrophy and local reactions at the site of injections (Galloway and Root, 1972; Teuscher, 1975). There have been reports of a reduction of the dose of insulin necessary for the maintenance of diabetic control on changing from standard to purified insulins. Reports of dose reduction has varied from 20 to 50% in different series, consisting mainly of adult diabetics (Bruni *et al.*, 1973; Evans and Smith, 1976; Logie and Stowers, 1976).

We present data on 21 diabetic children requiring >40 units per day of standard insulins in whom a change to monocomponent insulin led to a decrease in insulin requirements and better diabetic control.

Materials and methods

21 children (13 girls and 8 boys) who were unable to achieve satisfactory diabetic control despite high and increasing insulin dosage were changed from standard to monocomponent insulins. The mean age of the group was 7·9 years (range 3–13) and the mean duration of their diabetes from diagnosis was 5·2 years (range 1·5–12). Their treatment before the change is shown in Table 1. All children in this group were changed to a monocomponent porcine insulin (Monotard)* given as a single daily injection. During the 3 months before and 3 months after the change in insulin, diabetic control was measured by an analysis of home urine tests using the Clinitest† 2-drop method (Belmonte *et al.*, 1967), and the 24-hour urinary glucose excretion measured on a collection made at home.

Table 1 *The types and doses of standard insulins during the 3-month period preceding the change to monocomponent insulin*

Insulin regimen		*Make of insulin*	*No. of patients*	*Mean insulin dose*
Lente	o.d.	Unspecified	8	72
Rapitard	o.d.	Novo	7	78
Actrapid+Rapitard	b.d.	Novo	2	76
Rapitard	b.d.	Novo	1	88
Semi-Lente	o.d.	Unspecified	1	56
Isophane+soluble	b.d.	Nordisk	1	132
PZI+soluble	o.d.	Unspecified	1	76

Only 10 children were able to maintain their urine testing books in sufficient detail for an analysis of home urine tests to be made during the 3 months before and the 3 months after the change in insulin.

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Although the number of tests performed each day by individual children varied, the total number of tests made by these children during the 3 months before the change was 2188 and the total number of tests for the 3 months after the change in insulin was 2089.

Only 8 children were able to provide a 24-hour urine collection for glucose analysis before and after the change. Six of these children were among the 10 who had maintained home urine testing books satisfactorily.

The first 24-hour urine collection for glucose excretion was obtained at a mean time of 6·5 days (range 1–13) before the change to monocomponent insulin. The 2nd 24-hour urine collection was performed 9 weeks (range 3·5–13) after the change to monocomponent insulin.

The glucose content of the 24-hour sample was measured with a glucose analyser which uses glucose oxidase (Analox Instruments). The results are expressed in grams of glucose/24 hours.

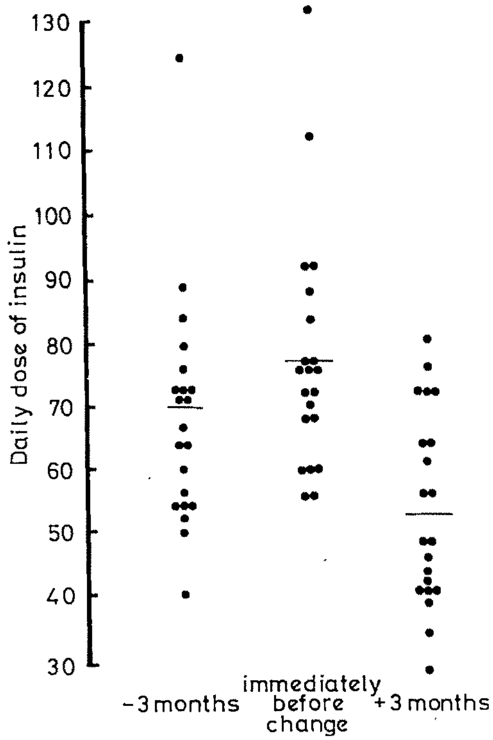

Figure *The total daily dose of insulin for the 21 children rose significantly during the 3 months before the change (paired t test P<0·001) and fell significantly during the 3 months after the change (P<0·001).*

Results

The insulin requirements in the 21 patients 3 months before the change in insulin, at the time of the change, and 3 months after the change, are shown in the Figure. During the 3 months preceding the change the daily dose of insulin rose from a mean of 70 units daily (range 40–124) to a mean of 77 units daily (range 56–132) (P<0·001 using the paired *t* test). In no case had the dose of insulin fallen over this period. During the 3 months after the introduction of monocomponent insulin the mean requirement fell to 53 units daily (range 27–82) (P<0·001 using the paired *t* test). This represents an average fall of 31% in the insulin requirement. In only one child did the insulin requirement actually increase after the change to monocomponent insulin, rising from 60–64 units. The biggest single fall was from 112 to 48 units (a fall of 64%).

An analysis of the home urine tests from 10 children before and after the change in insulin was also made. Taking all the tests available for each child before and after the change and classifying any tests with 0–½% glycosuria as 'good control' and 1–5% glycosuria as 'poor control' a 2 × 2 χ^2 table was drawn up for each patient. Five of the 10 children had significant improvements in their diabetic control with this method of evaluation (P<0·001). One child had a χ^2 value which just fell short of significance. The remaining 4 children had low χ^2 values, indicating no significant improvements in control.

The urine tests for the two 3-month periods were also compared in terms of the number of tests showing zero glycosuria at any time. Using the paired *t* test there was a significant increase in the total number of zero glycosuria tests after the change to monocomponent insulin (P<0·01) (Table 2).

Table 2 *A comparison of the total number of home urine tests using the 2-drop Clinitest method showing zero glycosuria during the 3 months before and 3 months after the change to monocomponent insulin. Using the paired t test there was a significant increase in the total number of zero glycosuria tests (P<0·01).*

Case	*Total no. of zero glycosuria readings*	
	On conventional insulin	*On monocomponent insulin*
1	95	116
3	0	6
5	12	137
6	51	102
7	92	132
8	110	167
9	19	50
10	3	16
11	11	22
12	8	36
Mean	40·1	78·4

The number of zero glycosuria tests before breakfast was considered as an indication of overnight diabetic control. Using the paired *t* test to compare the numbers 3 months before and 3 months after the insulin change there was a significant increase in the number of before-breakfast zero glycosuria tests after the change to monocomponent insulin ($P<0\cdot01$, Table 3).

In 8 children 24-hour urine collections were available as a measure of diabetic control before and after the change (Table 4). The mean glucose excretion before the change was 137 g/24h (range 1–426 g/24 h) which fell to a mean of 88 g/24 h (range 0–237 g/24 h) ($P<0\cdot01$ using the paired *t* test). Only one of these 8 patients showed an increase in glycosuria. The high value for the mean glucose excretion both before and after the change was because 4 of the 8 children had gross glycosuria on standard insulins which fell but failed to achieve reasonable levels by the time of the 2nd urine collection.

Table 3 *Comparison of the number of zero glycosuria tests before breakfast during the 3 months before and after the change to monocomponent insulin. Using the paired t test there was a significant increase in the number of such tests after the change ($P<0\cdot01$).*

Case	*No. of zero glycosuria readings before breakfast*	
	On conventional insulin	*On monocomponent insulin*
1	34	49
3	0	3
5	1	61
6	34	77
7	80	102
8	37	52
9	15	42
10	2	3
11	3	13
12	4	18
Mean	21·0	42·0

Table 4 *24-hour urine glucose excretion before and 3 months after the change to monocomponent insulin. The reduction in glucose excretion is significant ($P<0\cdot01$) using the paired t test.*

Case	*24-hour glucose excretion (g/24 hours)*	
	On conventional insulin	*On monocomponent insulin*
1	13·1	10·4
2	426·3	237·3
3	208·4	99·6
4	1·5	2·8
5	140·2	36·0
6	133·6	186·6
7	2·9	0·2
8	169·1	133·3
Mean	136·9	88·3

Discussion

The introduction of highly purified preparations of insulin represents an advance in the treatment of diabetics with lipo-atrophy at insulin injection sites. Many workers have observed a decrease in the insulin requirements of patients after a change to purified insulins (Evans and Smith, 1976; Logie and Stowers, 1976). This is in accord with the manufacturer's recommendations that, in patients requiring more than 40 units of insulin daily, the dose of insulin should be reduced by 20% at the time of the change (Novo Laboratories Ltd). The mean fall in insulin requirements of our patients was 31% during a 3-month period and some patients required further reductions subsequently. We had made a 10% reduction in the dose at the time of change to monocomponent insulin and subsequent reductions were made by the parents who had been warned of the likelihood of a reduced requirement. The parents judged this dose reduction by frequent home urine tests. In most cases the requirement began to fall after 2 weeks and continued to do so for a further 3–6 weeks. Many children had minor hypoglycaemic symptoms during this period and 2 children had major hypoglycaemic attacks, both suffering from early morning hypoglycaemic convulsions.

Comparative data on the quality of control achieved on changing from conventional to monocomponent insulins has been omitted in previous reports. Our results indicate that control was as good or better in most cases whether assessed clinically or by home urine tests or by 24-hour collections of urine for glucose excretion. Nevertheless the level of diabetic control achieved on monocomponent insulin was certainly not satisfactory at the time of reassessment in at least 4 of the children as judged by the persistently high 24-hour urinary glucose excretion.

Although the change of treatment is associated with the hazards of an uncertain reduction in the dose of insulin required, we do not feel that this constitutes a contraindication to the change provided that this likelihood is appreciated. We feel that all new diabetic children should be started on highly purified insulins and that established diabetic children should be changed on to highly purified insulins because of the reduced incidence of lipo-atrophy (Teuscher, 1975), the reported reduction in insulin antibody levels (Oakley, 1976), and because we believe that insulin should, as far as possible, be free from other protein contaminants as it is to be administered to the child for life.

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Interferon synthesis by human colostral leucocytes

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SUMMARY The antiviral potential of human colostral leucocytes was assessed by their capacity to produce interferon. Leucocytes cultured from colostrum were stimulated by mitogens or Newcastle disease virus (NDV) to produce interferon which, by metabolic and physicochemical criteria, corresponded to normal human leucocyte interferon. Prepartum cells produced higher levels than postpartum cells. Colostral cells were less efficient producers than blood leucocytes.

Human colostrum and breast milk contain inhibitors for a variety of viruses (Sabin and Fieldsteel, 1962; Shortridge *et al.*, 1974; Matthews *et al.*, 1976). The presence of interferon in human colostrum or milk has not been conclusively demonstrated, although colostral leucocytes are known to be able to synthesise interferon-like material in response to stimulation (Emödi and Just, 1974; Lawton and Shortridge, 1977).

In view of the current interest in the function of these cells and their possible contribution to neonatal defences in breast feeding, we have investigated further the capacity of colostral cells to synthesise interferon when stimulated by mitogens and inactivated NDV. We also report the results of our characterisation of this substance.

Materials and methods

Preparation and culture of colostral cells. Colostrum samples were obtained from 26 women, mainly Chinese, by manual expression into sterile plastic universal bottles. 11 samples were prepartum and 15 were 2 to 5 days postpartum. Samples were diluted 1:1 in Hank's balanced salt solution (HBSS), centrifuged at 110 × *g* for 10 min and the pellet washed twice in HBSS before counting the cells in a haemocytometer. Total cell counts in colostrum ranged from 0·6 to 11 × 10^9/l (600 to 11 000/mm^3) mean 3·37 × 10^9/l (3370/mm^3). Differential counts were performed on stained cytocentrifuge preparations; macrophages made up 11–94% (mean 57%), polymorphonuclear leucocytes (PMNs) 2–87% (mean 33%), and lymphocytes 1–39% (mean 9·6%).

After counting, the cells were resuspended at a concentration of 2 × 10^9 cells/l (2000/mm^3) in leucocyte growth medium (LGM) comprising RPMI-1640 (Gibco) supplemented with 20% heat-inactivated human AB serum, glutamine 2 mmol/l, penicillin 100 U/ml, and streptomycin 100 µg/ml. One ml volume of cell suspension was dispensed into Nunc tissue culture tubes; the total number of cells obtained from the colostrum sample (usually about 15 × 10^9/l (15 000/mm^3)) limited the number of replicate cultures that could be performed. Mitogens known to stimulate leucocyte interferon synthesis were added to the cultures in predetermined optimal doses; PHA-P (Difco) 5 µl/ml, Conconavolin-A (Sigma) 40 µg/ml. Cells were also preincubated for 30 min with an optimal dilution of a lentogenic (avirulent) strain of NDV (D2/75) and then washed 3 times before resuspending in LGM for culture. Each experiment included an unstimulated control culture. Cultures were incubated at 37°C for 72 hours. The supernatants were harvested and replicate supernatants pooled before being assayed for interferon activity. Supernatants were routinely stored frozen at −20°C, but for periods of less than 24 hours they were held at 4°C.

Interferon assay. The assay was based on that of Havell and Vilček (1972) using human diploid foreskin fibroblasts in Linbro micro T/C plates. Fibroblasts were challenged with vesicular stomatitis virus (VSV) after 24-hour exposure to culture supernatants and the titre of interferon was expressed as the reciprocal of the highest protective dilution. A standard interferon preparation (13 000 NIH units/

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ml) consistently gave a titre of 50 000. Samples were titred at trebling dilutions beginning at 1/5 and assayed in duplicate.

Dialysis of samples before assay did not alter the interferon titre but it did reduce the cytotoxic effect on fibroblasts which was sometimes observed at low dilutions (1/5 or 1/15). Therefore predialysis of samples at pH 2 was adopted as standard procedure (see below, acid dialysis). Samples containing Con-A tended to be more toxic to the fibroblasts at low dilutions and this effect was not removed by dialysis. Consequently Con-A was often omitted and Con-A supernatants were not used in the characterisation studies even though it tended to induce higher interferon levels than PHA or NDV.

Comparison of colostral cells and autologous blood leucocytes. In 7 cases autologous blood leucocytes were cultured in parallel with the colostral cells to compare their capacities to synthesise interferon-like substances *in vitro*.

Blood lymphocytes were separated from heparinised blood over Ficoll/Hypaque, washed 3 times in BSS, counted and resuspended in LGM at 2 × 10^9 cells/l (2000/mm^3). The suspensions contained 5–15% monocytes. The blood mononuclears were stimulated with PHA and NDV as described for colostral cells. After 72 hours' incubation the supernatant was harvested and assayed for interferon activity.

Characterisation studies. High titre supernatants of PHA- or NDV-stimulated cultures were pooled and studied as follows:

Metabolic characterisation
This was based on the fact that the protective effect of interferon requires intact mechanisms of RNA and protein synthesis in the cells on which protection is to be conferred (Ng and Vilček, 1972).

To inhibit RNA synthesis fibroblasts were pretreated with actinomycin D (0·5 and 1·0 μg/ml in culture medium) for 30 min at 37°C then washed 3 times in HBSS before adding the pooled supernatant. To inhibit protein synthesis cycloheximide was diluted in culture medium to 100 μg/ml and this medium was used as diluent for the pooled supernatant. Cells exposed to cycloheximide were washed 3 times in HBSS before virus challenge. Supernatant was also assayed on control cells not exposed to metabolic inhibitor. Each group included appropriate positive and negative controls for virus cytopathic effect.

Physiocochemical characterisation
Supernatant aliquots were treated as described below before assay.

Acid dialysis. Supernatants were dialysed against 0·1 mol/l KCl, pH 2, at 4°C for 18 hours, then against phosphate buffered saline (PBS), pH 7·4, for 4 hours. Control supernatants were dialysed for 22 hours against PBS only.

Freeze-thaw, heat, and trypsinisation. Respective aliquots were frozen to −70°C and thawed 5 times, heated to 56°C for 30 min, or incubated in the presence of trypsin (1·25 mg/ml) at 37°C for 5 hours. A control aliquot was kept at 4°C.

Detection of sialic acid residues. Pooled supernatant of known titre was applied to a column of immobilised neuraminidase at pH 4·5. The column was developed by elution with 0·1 mol/l/acetate buffer in 0·5 mol/l NaCl, pH 4·5, followed by 0·1 mol/l bicarbonate in 0·5 mol/l NaCl, pH 9·0. The eluted protein peaks (0D 280 nm) were collected and tested for interferon activity (Fung and Ng, 1978).

In the interferon characterisation experiments supernatants were titred at trebling dilutions.

Results

Table 1 shows the geometric mean titres of interferon in the colostral cell cultures. Two PHA supernatants (>135) were not titred to the endpoint; these were taken as 135 and all negative samples (<5) were taken as 1 for purposes of calculation. The highest interferon titre obtained was 640 in a Con-A stimulated culture from a prepartum sample. The combined results (pre- and postpartum) show that Con-A gave the highest mean interferon activity, while NDV, although less efficient than Con-A, was a more efficient inducer than PHA. All unstimulated control cultures were negative for interferon activity (titre <5).

Prepartum colostral cells produced higher interferon levels than postpartum cells; this was so for

Table 1 *Interferon activity in colostral cell culture supernatants*

	PHA stimulated	*Con-A stimulated*	*NDV stimulated*	**All inducers*
Prepartum	11 (1–320) n = 11	59 (1–640) n = 3	38 (15–135) n = 7	21 (1–640) n = 21
Postpartum	7·6 (1–135) n = 15	24 (1–135) n = 6	12 (1–45) n = 8	11 (1–135) n = 29
All cultures (pre- and postpartum)	9·7 (1–320) n = 26	32 (1–640) n = 9	19 (1–135) n = 15	

The results are expressed as geometric mean titres of 72-hour culture supernatants with titre ranges in parentheses. Differences between mean titres of pre- and postpartum cultures did not reach significance at the 5% level (2-tailed Student's *t* test). Unstimulated control cultures were negative (titre <5) in all experiments.
*Pooled data for the 3 inducers.

each inducer but even when data were pooled (Table 1) the difference was not significant at the 5% level ($0{\cdot}15>P>0{\cdot}1$). This difference could not be explained by the relative proportions of cell types in the cultures; the mean percentages of macrophages, lymphocytes, and PMNs in prepartum and postpartum colostrum were very similar and the overall data showed no clear correlation between interferon titres and the proportions of cell types in the original culture inocula.

Colostral cells and autologous blood leucocytes. The geometric mean titres of interferon from these paired cultures are set out in Table 2. The capacity of blood mononuclears to synthesise interferon in response to NDV stimulation was significantly higher than that of colostral cells ($P<0{\cdot}025$), whereas the difference in response to PHA did not reach a level of significance ($P>0{\cdot}15$).

Table 2 also shows that NDV was clearly a more efficient inducer of interferon in blood leucocytes than was PHA (ratio, 8·5:1), whereas colostral cells demonstrated little difference in response to these two inducers.

Interferon characterisation. The results of the characterisation studies are summarised in Table 3. Inhibitors of RNA and protein synthesis both abrogated the protection of fibroblasts by the culture supernatants, consistent with the protective effect being due to interferon.

Activity was not dialysable; it was stable at pH 2 and destroyed by trypsin. PHA-induced activity was stable to freeze–thaw and relatively heat stable. On the other hand, NDV-induced activity was relatively freeze–thaw stable and heat labile.

Table 2 *Interferon activity in colostral cell and autologous blood leucocyte cultures*

	PHA-stimulated		*NDV-stimulated*	
Colostral cells	16 (1–135)	$P>0{\cdot}15$ (n = 7)	18 (5–45)	$P<0{\cdot}025$ (n = 6)
Autologous blood leucocytes	10 (1–45)		85 (15–415)	

The results are expressed as geometric mean titres of 72-hour culture supernatants with titre ranges in parentheses. P values were computed by the Student's *t* test for correlated data. Unstimulated control cultures were negative (titre <5) in all experiments.

Interferon activity induced by NDV bound to a column of immobilised neuraminidase at acid pH via its N-acetyl-neuraminic acid residues and could be recovered essentially without loss of activity by elution at pH 9·0.

Discussion

Recent studies have shown that leucocytes in colostrum may play an important role in transferring specific and nonspecific host resistance factors to the neonate (Murillo and Goldman, 1970; Ahlstedt *et al.*, 1975; Parmely *et al.*, 1976; Pitt *et al.*, 1977; Schlesinger and Covelli, 1977). Our results confirm that colostral leucocytes can synthesise interferon under appropriate conditions and that their capacity to do so is comparable with that of blood leucocytes (Emödi and Just, 1974).

Interferon protects a cell by first inducing the synthesis of an antiviral protein (Joklik, 1977) and this process is dependent on intact mechanisms of RNA and protein synthesis (Ng and Vilček, 1972). It was found that the antiviral effect observed in our experiments was dependent on (1) pretreatment of cultures with supernatant, and (2) intact macromolecular synthesis of the fibroblasts. It was further shown that the antiviral substance was nondialysable, resistant to treatment with acid, stable to freeze–thaw, destroyed by trypsin, and it appeared to have sialic acid residues which bound it to immobilised neuraminidase. These are all known properties of interferon.

Surprisingly, this interferon was unlike classical human leucocyte interferon (type I) in being relatively heat labile. Haahr *et al.* (1976) showed that the presence of fully differentiated macrophages resulted in the production of heat-labile (type II) interferon by human lymphocytes. Therefore the high proportion of mature macrophages in colostral leucocyte cultures may account for heat-labile interferon synthesis. Because our colostral cells contained a mixture of lymphocytes (usually <10%) and macrophages, it is difficult to draw any conclusions about

Table 3 *Metabolic and physicochemical characterisation of interferon activity*

	Actinomycin-D 0·5 µg/ml	*Cycloheximide 100 mg/ml*	*Dialysis pH 2*	*Freeze-thaw*	*Heat*	*Trypsin*	*Sialic acid residues*
PHA-induced	Not done	+	−	−	±	+	Not done
NDV-induced	+	+	−	±	+	+	Present

Supernatants titred at trebling dilutions.
− Denotes stability; ± denotes reduction in activity of one dilution; + denotes reduction in activity of more than one dilution (or abrogation of interferon effect by metabolic inhibitors).

the principal cell of origin of the interferon activity. Human interferon is known to be heterogeneous with respect to the cell of origin and to the type of inducer (Vilček *et al.*, 1977); it is likely, therefore, that the active material in our cultures represented a mixture of 'interferons'.

It is of interest that prepartum colostrum leucocytes showed a greater capacity to produce interferon than did postpartum cells. This difference could not be related to the very small differences in proportions of cell types in the cultures; the reason for it remains unknown.

Emödi and Just (1974) and Matthews *et al.* (1976) were unable to detect free interferon-like activity in human colostrum or breast milk. We have been able to detect interferon-like activity in a small proportion of the samples of colostrum and breast milk which we have tested (unpublished observations) and work is in progress to characterise it. It is not yet clear whether this activity is related to infection in the mother.

The important implication of our findings is that since colostral leucocytes under appropriate conditions can produce interferon, they may thereby confer on the suckling infant protection against viral infection.

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Duodenal bile acids in infants with protracted diarrhoea

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SUMMARY Bile acids were estimated in the duodenum of infants with protracted diarrhoea and compared with those in a control group. Significantly lower levels of total bile acids were found in infants with protracted diarrhoea, a finding which may be due to ileal dysfunction. Low concentrations of total bile acids may contribute to the poor nutritional state of these patients by impairing the normal digestion and absorption of dietary fat and fat-soluble vitamins. The absence of deconjugated bile acids in the duodenal juice of most infants with protracted diarrhoea suggests that they do not contribute significantly to the pathophysiology of this disorder.

Protracted diarrhoea of infancy is a severe and debilitating disorder, characterised by the passage of at least 4 loose stools a day for more than 2 weeks. In some infants protracted diarrhoea is secondary to recognised gastrointestinal diseases (Larcher *et al.*, 1977), while in others the pathogenesis remains unknown. The patients become dehydrated and malnourished due to persistent fluid loss and to difficulty in maintaining an adequate oral intake of food. Impaired digestion and absorption, resulting from a damaged small intestinal mucosa, also contribute to the poor nutritional state. As recovery of small intestinal mucosal function may be delayed by malnutrition, a vicious cycle of events occurs which perpetuates the clinical problem, and intravenous nutrition may be needed to sustain life.

Bile acid studies on infants with protracted diarrhoea have shown two principal abnormalities, either of which could contribute to the pathophysiology of this disorder. Deconjugated bile acids were detected in the duodenal juice of some infants (Gracey *et al.*, 1969), while in experimental animals the same bile acids had cytopathic effects on the small intestinal mucosa (Dawson and Isselbacher, 1960), and inhibited the absorption of water, electrolytes, and monosaccharides from the lumen of the small intestine (Gracey *et al.*, 1971; Harries and Sladen, 1972). Increased faecal excretion of bile acids has also been shown in infants with protracted diarrhoea (Balistreri *et al.*, 1977). If the loss is prolonged, it may reduce the size of the bile acid pool and lower the concentration of bile acids in the small intestine. As bile acids are essential for the optimal absorption of dietary fat and fat-soluble vitamins, a fall in concentrations below the level at which micelle formation occurs in the small intestine might further compromise the poor nutritional state of the patient. Bile acids in the duodenum of a control group of infants (group A) were therefore compared with those in a group of infants with protracted diarrhoea (group B).

Materials and methods

Patients. The infants were divided into two groups (Table 1). Infants with protracted diarrhoea (group

Table 1 *Clinical details of infants studied*

Cases	*Age (weeks)*	*Sex*	*Diagnosis*
Group A (controls)			
1	2	M	Inguinal hernia
2	5	F	Feeding problem
3	8	M	Congenital heart disease
4	8	M	Congenital heart disease
5	12	F	Feeding problem
Group B (patients)			
6	6	M	Protracted diarrhoea
7	6	M	Protracted diarrhoea + secondary glucose intolerance
8	8	M	Protracted diarrhoea + secondary lactose intolerance
9	8	F	Protracted diarrhoea
10	12	F	Protracted diarrhoea + secondary glucose intolerance

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B) had been passing at least 4 loose stools daily for more than 2 weeks, without the isolation of known enteropathogenic bacteria. Stools were tested for the presence of reducing substances using Clinitest tablets (Kerry and Anderson, 1964), and significant amounts (>0·5%) were detected in 3 of them. The presence of glucose was confirmed by paper chromatography in 2 patients and lactose in one. All the infants in the control group (group A) needed tube feeding as a normal part of their medical care, and none had diarrhoea. As concentrations of duodenal bile acids have been shown to increase with age in early infancy (Challacombe *et al.*, 1975), these infants were of approximately similar ages as those in group B.

Sampling regimen. Duodenal juice was obtained by the use of a long polyethylene feeding catheter (Argyl, 5 FG, 91 cm), weighted with a gold bead (Rhea and Kilby, 1970). The distal end of the tube was allowed to pass into the duodenum by normal peristalsis and its position in the 2nd to 4th part of the duodenum was confirmed by screening. The first sample of duodenal juice aspirated was discarded to exclude contamination by gastric juice and the 2nd sample was placed in a sterile container and stored at −20°C until analysed. Samples were taken 2 hours after a full cream cows' milk formula feed in group A and 2 hours after a 5% glucose feed in group B. The absence of significant differences in duodenal bile acid concentrations in infants 2 hours after either type of feed has been previously demonstrated (Challacombe *et al.*, 1975).

Bile acid analysis. Bile acids were estimated using sulphuric acid fluorescence after separation by thin layer chromatography (Panveliwalla *et al.*, 1970). Total and individual bile acids were measured in samples of duodenal bile from both groups of infants. Separate estimates of the individual taurine and glycine conjugated dihydroxy bile acids were not made because it was not possible to separate them by the chromatographic method.

Results

The results of bile acid analyses are shown in Table 2. The difference between mean values of total bile acids, taurine, and glycine conjugates, and individual bile acids in group A and group B were examined for statistical significance using Student's *t* test. Differences were regarded as significant when P values were $<0\cdot05$.

Concentrations of total bile acids were significantly lower in infants in group B ($P<0\cdot01$). This finding was mainly due to lower mean concentrations of taurocholic ($P<0\cdot01$) and glycocholic acids ($P<0\cdot05$). Ratios of total glycine conjugates to total

Table 2 *Duodenal bile acids (mmol/l)*

Cases	*Total bile acids*	*Conjugates*			*Deconjugated bile acids*	*Taurocholic acid*	*Taurine conjugated dihydroxy bile acids*	*Taurolithocholic acid*	*Glycocholic acid*	*Glycine conjugated dihydroxy bile acids*
		Glycine	*Taurine*	*Glycine/Taurine*						
Group A (controls)										
1	5·4	1·4	3·9	0·3	—	1·6	2·3	ND	1·0	0·5
2	7·1	4·0	3·0	1·3	—	1·4	1·1	0·5	3·1	1·0
3	9·1	6·3	2·8	2·2	—	1·4	1·1	0·3	3·1	3·2
4	6·1	5·0	1·0	5·0	—	0·4	0·3	0·4	3·6	1·4
5	9·8	6·4	3·3	1·9	—	1·3	1·3	0·7	3·9	2·5
Mean	7·5	4·6	2·8	2·2	—	1·2	1·2	0·4	2·9	1·7
SD	1·9	2·0	1·1	1·7	—	0·5	0·7	0·2	1·1	1·1
Coefficient of variation (%)	25	43	38	80		38	57	66	39	64
Group B patients										
6	2·1	1·6	0·6	2·6	—	0·5	0·1	ND	1·6	ND
7	7·1	4·9	2·2	2·2	—	0·5	1·3	0·4	2·4	2·5
8	2·8	1·6	0·2	8·0	0·9	ND	0·2	ND	1·3	0·4
9	1·4	0·6	0·8	0·7	—	0·2	0·3	0·2	0·7	ND
10	2·1	1·0	1·1	0·9	—	0·4	0·5	0·2	0·6	0·4
Mean	3·1	1·9	1·0	2·9	—	0·3	0·5	0·2	1·3	0·6
SD	2·3	1·7	0·7	2·9	—	0·2	0·5	0·2	0·7	1·0
Coefficient of variation (%)	74	89	75	103		62	100	100	53	173
t	3·3	2·3	3·2	0·46		3·8	1·9	1·6	2·7	1·6
P	<0·01	<0·05	<0·01	>0·3		<0·01	>0·05	>0·1	<0·05	>0·1

ND = not detected.

Conversion: SI to traditional units—Taurocholic acid: 1 mmol/l ≈ 51·5 mg/100 ml. Taurine conjugated dihydroxy bile acids: 1 mmol/l ≈ 49·9 mg/100 ml. Taurolithocholic acid: 1 mmol/l ≈ 43·8 mg/100 ml. Glycocholic acid: 1 mmol/l ≈ 46·5 mg/100 ml. Glycine conjugated dihydroxy bile acids: 1 mmol/l ≈ 44·9 mg/100 ml.

taurine conjugates (G/T) were not significantly different in the two groups. Mean concentrations of taurine conjugated dihydroxy bile acids, glycine conjugated dihydroxy bile acids, and taurolithocholic acid were also not significantly different. In group B taurocholic acid was present in 4 out of 5, taurolithocholic acid in 3 out of 5, and glycine conjugated dihydroxy bile acids in 3 out of 5 infants. In group A all bile acids were present with the exception of taurolithocholic acid which was not detected in one patient. Deconjugated bile acids were not detected in infants in group A, but cholic acid (0·13 mmol/l; 5·3 mg/100 ml), chenodeoxycholic acid (0·57 mmol/l; 22·3 mg/100 ml), and lithocholic acid (0·25 mmol/l; 9·4 mg/100 ml) were found in the duodenal juice of one infant in group B who had secondary lactose intolerance. In this infant, who has been previously reported (Challacombe *et al.*, 1974a), *Bacteroides* sp. (obligate anaerobes with known bile acid deconjugating properties *in vitro*) were isolated from the duodenal juice.

Discussion

Concentrations of total bile acids were significantly lower in the duodenum of infants in group B compared with group A. Morphological and functional changes in the bowel may interrupt the enterohepatic circulation of bile acids leading to increased bile acid excretion in the faeces. The liver initially compensates for the increased faecal loss by increased synthesis, but eventually synthesis is inadequate, leading to a depleted bile acid pool and to low levels of bile acids in the duodenum. There is some experimental evidence in favour of this proposed mechanism. The oral or intravenous administration of radioactively-labelled bile acids to adults with diffuse ileal disease leads to rapid excretion of the radioactive label in the faeces (Meihoff and Kern, 1968). Oral administration of C^{14}-cholic acid to infants with ileal resections and to infants with protracted diarrhoea also results in increased faecal excretion of this label (Balistreri *et al.*, 1977). The presence of ileal dysfunction in protracted diarrhoea is further suggested by abnormal Schilling tests for vitamin B12 absorption (Balistreri *et al.*, 1977). Impaired ileal function may be the result of associated mucosal damage. Severe mucosal changes have been reported in the upper small intestine (Greene *et al.*, 1975) and these may be sufficiently extensive to involve the terminal ileum where most bile acid reabsorption should occur. Ileal dysfunction may also contribute to the protracted diarrhoea in these patients, as excessive amounts of dihydroxy bile acids reaching the colon have been shown to provoke excessive water secretion by the colonic mucosa (Mekhjian *et al.*, 1971).

A higher ratio of glycine to taurine conjugates in duodenal bile is usually present in adults with terminal ileal disorders (Heaton *et al.*, 1968), a finding which may be due to the relative scarcity of taurine or of its precursor cysteine, in the face of an increased demand for bile acid conjugation. Mean values of the glycine/taurine ratio were not significantly raised in patients with protracted diarrhoea compared with the controls. As bile acids are mainly conjugated with taurine in early infancy, failure to demonstrate consistently raised glycine/taurine ratios in patients with protracted diarrhoea may be due to an increased availability of taurine for conjugation.

Trihydroxy bile acid concentrations were significantly lower in infants in group B compared with group A, and mean concentrations of dihydroxy bile acids were also low, but the values did not reach statistical significance. In adults with ileal resections the absorption of both dihydroxy and trihydroxy bile acids has been shown to be equally impaired (Low-Beer *et al.*, 1974). Although ileal dysfunction may be one explanation for the bile acid findings reported in protracted diarrhoea, further study of the enterohepatic circulation and faecal excretion of bile acids in this disorder will be necessary. Bacterial overgrowth in the upper small intestine (Gracey and Stone, 1972; Challacombe *et al.*, 1974b), a rapid small intestinal transit time, or impaired synthesis of bile acids by the liver due to malnutrition, could each influence bile acid metabolism in infants with protracted diarrhoea.

The deconjugated bile acids, deoxycholic and chenodeoxycholic acids, have been shown to have cytopathic and metabolic-inhibitory effects on the small intestine of experimental animals (Dawson and Isselbacher, 1960; Low-Beer *et al.*, 1970; Gracey *et al.*, 1971; Harries and Sladen, 1972), and these bile acids could have similar effects in patients with protracted diarrhoea and monosaccharide malabsorption (Gracey *et al.*, 1969). Cholic, chenodeoxycholic, and lithocholic acids were detected in small quantities in only one infant with protracted diarrhoea, an infant who was also intolerant of oral lactose. These findings suggest that deconjugated bile acids were not important in the pathophysiology of protracted diarrhoea in our patients, but samples were taken from a single site only in the duodenum, and sampling from other sites will be necessary before the contribution of deconjugated bile acids can be fully evaluated. Concentrations of total bile acids in the duodenum of 4 of the 5 infants in group B were below a level of 4 mmol/l. Badley *et al.* (1969) have shown that total bile acid concentrations in the upper small intestine should exceed this value for optimal fat absorption to occur. The digestion and absorption of dietary fat and fat-soluble vitamins may therefore be impaired in patients with protracted diarrhoea, and absorption and nutrition may be improved by the use of medium chain triglycerides, which are well absorbed in the absence of bile acids.

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Familial partial trisomy of the long arm of chromosome 3 (3q)

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SUMMARY A case of partial trisomy of the long arm of chromosome 3 (3q21→qter) is described. The clinical findings are compared with those in 5 previously reported cases. There is hirsutism and characteristic facial dysmorphism, the common features of which are a square-shaped face, prominent nasal bridge, everted nostrils, hypertelorism, and palate abnormalities; occurring less often are abnormalities of vertebrae, thorax, and digits, or cardiovascular, urinogenital, and central nervous system. New features noted in this present case are absence of right eye from orbit and spina bifida. The spectrum of this syndrome is discussed, with possible relation to the degree of trisomy. The present case is the 6th to be reported with partial trisomy of the long arm of chromosome 3.

Case report

The propositus (Fig. 1) was the result of a 3rd pregnancy of the mother; she had had 2 phenotypically normal children from a previous marriage. The pregnancy was noted for small fetal size, lack of intrauterine movements, and recurrent small antipartum haemorrhages. Urinary oestriol excretion was low throughout the pregnancy. The child was delivered by emergency caesarean section when the mother presented in labour with a fetal heart rate of 80.

The child, a girl, with multiple congenital anomalies, died soon after delivery. Clinical features included: a square-shaped face; wide nasal bridge and everted nostrils; small malformed and malpositioned ears; absence of right eye; high arched palate; a short webbed neck; clinodactyly of the 5th fingers; lumbar meningomyelocele with congenital dislocation of both hips, and bilateral talipes equinovarus. *X*-ray of the chest showed hypoplasia of the right first rib.

Necropsy (Guy's Hospital, no. 362/76) (Dr J. Heaton) showed absence of the roof of the right orbit and the dysplastic right eye was found in the anterior cranial fossa. Large anterior and posterior sagittal fontanelles separated the bones of the vault of the skull. The brain (250 g) was sectioned to show diffuse dilatation of the ventricular system consistent with internal hydrocephalus. There was a large atrial septal defect. The left kidney and part of the right kidney showed pin-point sized cysts which were visible both externally and on the cut surfaces. There were also bilateral double ureters draining the cystic dysplastic kidneys; on the left side both were severely dilated and kinked; on the right only one was dilated.

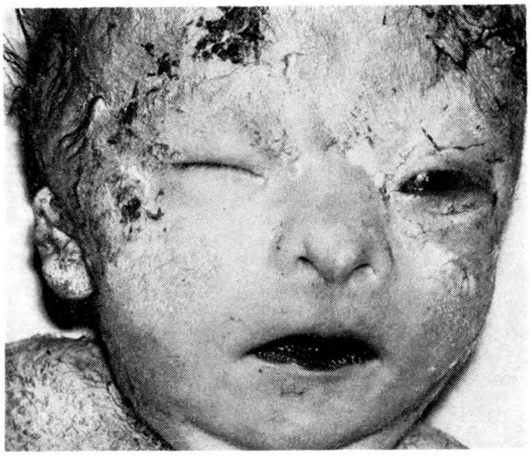

Fig. 1 *The propositus, note square-shaped face, malformed ears, absence of right eye.*

Chromosome studies. Chromosomes prepared from cultured skin fibroblasts and lymphocytes from the

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propositus were either banded with trypsin and stained with Geimsa (G bands) or stained with quinacrine mustard to give Q bands. Analysis showed additional chromosomal material on the long arms of no. 13 (Fig. 2c). Subsequent studies of the mother's chromosomes showed a balanced translocation between the long arms of nos 3 and 13 (Fig. 2a), which may be expressed as: 46,XX,t (3;13) (q21;q34), and the child's unbalanced chromosome constitution as: 46,XX,der(13), t(3;13) (q21;q34) mat. The propositus therefore had 2 normal chromosomes no. 3 and an abnormal no. 13 to which a large additional segment of the long arm of no. 3 was attached, with slight loss of the terminal region of 13q.

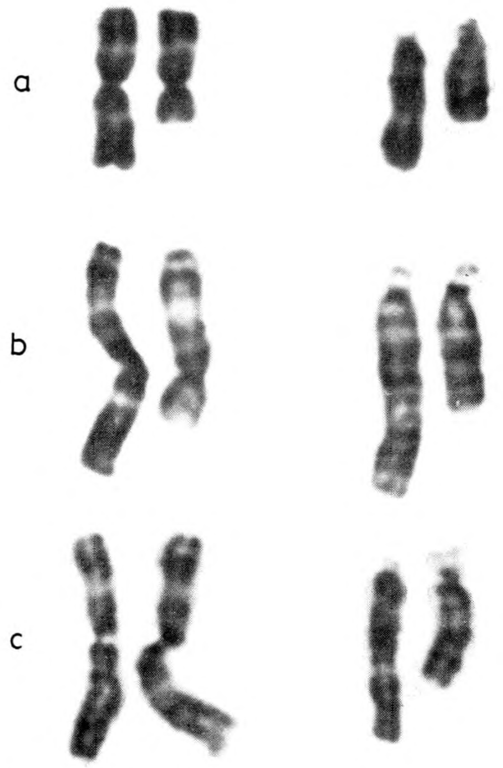

Fig. 2 (*a*) *balanced chromosomes mother t(3;13) (q21;q34);* (*b*) *balanced chromosomes daughter t(3;13) (q21;q34);* (*c*) *unbalanced chromosomes propositus der(13)t(3;13) (q21;q34)mat.*

One of two sisters carried the translocation in the balanced form (Fig. 2b) and the other sister had a normal female chromosome complement.

The maternal great-grandparents (Fig. 3) (I,3 and I,4) had 17 children, 10 of whom died neonatally. The maternal grandmother (II,9) had 3 miscarriages out of 7 pregnancies, while the maternal aunt (III,4) had 3 miscarriages and one neonatal death from 4 pregnancies and was then sterilised. The index family has two phenotypically normal children and the propositus.

In three generations about half the number of babies known to have been conceived had survived pregnancy. The losses were attributable to miscarriage and neonatal death and it is probable that most were the result of the translocation in an unbalanced form. However, there are no details of these except that at least 6 were miscarriages.

Discussion

Table 1 lists the features of 5 known cases of partial trisomy 3q and a 6th case (Clarke *et al.*, 1964) in which there was no banding information but as the clinical features were similar it is felt that there is justification for its inclusion. All have in common the square-shaped face with prominent nasal bridge

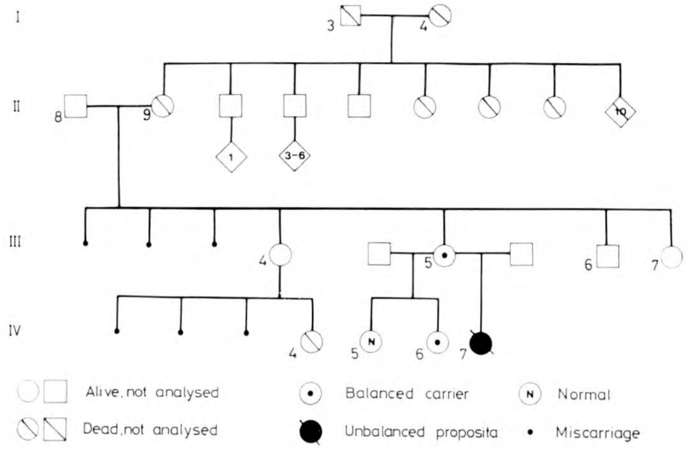

Fig. 3 *Family tree.*

Table 1 *Findings in 6 cases of partial trisomy of long arm of chromosome 3*

	Present case	*Chiyo (1976)*	*Hirschhorn (1973)*	*Schwanitz (1977)*		*Clarke (1964)*
				1	*2*	
Sex	F	F	M	M	M	F
Age				Alive 10+ years	Alive 3+ years	Alive 7+ years
At death (days)	1	32	Neonate			
Duplication	(3q21→ qter)	(3q21→ qter)	(3q21→ q21)	(3q25→ qter)		*
CNS						
Gross brain abnormality	+	+	+			
Spina bifida	+					
Epilepsy/ hypotonia				+	+	+
Face						
Square-shaped	+	+	?*	+	+	+
Malformed low set ears	+	+	?*	+	+	
Prominent nasal bridge and everted nostrils	+	+	?*	+	+	+
Palate abnormality	+	+	+	+	+	+
Micrognathia	+	+	+	+	+	+
Hypertelorism	+	+	+	+	+	
Rudimentary eye	+					
Hirsutism	+	+	+	+	+	
Skeletal						
Short neck	+	+				+
Clinodactyly	+	+		+	+	+
Foot abnormality	+			+	+	+
Thoracic and vertebral	+			+		+
Cardiac						
CHD	+	+	+			
Urinogenital						
Cryptorchidism				+	+	
Uterus bicornis		+				
Double ureter	+		+			
Renal cortical cysts	+	+				

*Not described.

Table 2 *Chromosome abnormalities in 5 infants with partial trisomy of long arm of chromosome 3, and in their parents*

Present case		
Balanced	Mother	46,XX,t(3;13) (q21;q34)
Unbalanced	Neonatal death	46,XX,der(13),t(3;13) (q21;q34) mat
Chiyo *et al.* (1976)		
Balanced	Mother	46,XX,t(2;3) (p25;q21)
Unbalanced	Neonatal death	46,XX,der(2),t(2;3) (p25;q21)mat
Hirschhorn *et al.* (1973)		
Balanced	Father	46,XY,inv(3) (p25;q21)
Unbalanced (meiotic recombination)	Stillbirth	46,XY,rec(3),dup q,inv(3) (p25;q21)
Schwanitz *et al.* (1977)		
Balanced	Mother	46,XX,t(3;22) (q25;p11)mat
Unbalanced	Cases 1 and 2 alive	46,XY,der(22),t(3;22) (q25;p11)mat
Clarke *et al.* (1964)		
Balanced	Mother	46,XX,t(3/C)
Unbalanced	Daughter alive	46,XX, –C, +Cq+ (no banding data available)

everted nostrils, hirsutism, hypertelorism, and palate abnormalities. Other features present in decreasing frequency are micrognathia, malformed low-set ears, clinodactyly, foot abnormalities, webbed neck, thoracic and vertebral defects, and urinogenital abnormalities. Features noted in isolation include deafness, cataracts, abnormal thumb insertion, syndactyly, short 5th metacarpal (Schwanitz *et al.*, 1977). Clarke *et al.* (1964) and Schwanitz *et al.* (1977) also noted hyperextensible joints and bilateral single palmar creases. Features in the present case not previously described are microphthalmia and meningomyelocele.

In these 6 cases of partial trisomy 3q, 3 died neonatally (present case; Hirschhorn *et al.*, 1973; Chiyo *et al.*, 1976) and 3 survived into childhood (Clarke *et al.*, 1964; Schwanitz *et al.*, 1977). The survivors did not have the gross abnormalities of heart and brain which were incompatible with life but they all had hypotonia, epilepsy, and moderate mental retardation.

The reported cases, and our own, had unbalanced chromosome abnormalities which resulted from structural anomalies in a carrier parent (5 maternal, 1 paternal) (Table 2). An inversion was present in one (Hirschhorn *et al.*, 1973) and the remaining 5 were the result of reciprocal translocations involving 3q with other chromosomes. Nevertheless, we note that 3 cases have similar break points (3q21) (Hirschhorn *et al.*, 1973; Chiyo *et al.*, 1976; present case). It may be significant that they have a similar clinical pattern. Two of the milder cases, brothers, had a more distal break point (3q25) and are therefore trisomic for a smaller portion of 3q (Schwanitz *et al.*, 1977). In the 6th case (Clarke *et al.*, 1964) the actual break points were not established.

The only important factor is the duplication of 3q; the deficiencies of the other chromosomes are slight, since only their terminal bands are involved, present case (13q34), Chiyo (2p25), and Schwanitz (the heterochromatic regions of 22p, which are generally thought to be genetically inert). In Hirschhorn's case the 3 alone is involved and the details of the break points in Clarke's case are not known.

From such a small group of cases the range of abnormalities associated with partial trisomy 3q cannot be defined. The features common to these cases provide a characteristic facial appearance by which others may be suspected, but a chromosomal diagnosis should always be established.

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Hepatic dysfunction in childhood malaria

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SUMMARY Hepatic function of 80 children aged under 3 years with *Plasmodium vivax* malaria were studied during the acute attack and 6 weeks after antimalarial treatment. Raised levels of serum aspartate transaminase (serum AST; SGOT), serum alanine transaminase (serum ALT; SGPT), and alkaline phosphatase were observed in 68%, 39%, and 46% of cases respectively. AST levels were higher than ALT ones and the mean level of both enzymes was much higher in patients with hepatomegaly. The hepatic dysfunction which these observations reflect is transient, as these enzymes were found to be at their normal levels 6 weeks after treatment. A transient derangement of liver function is thus a common feature of childhood malaria, and hepatic dysfunction takes place to a significant degree even in *P. vivax* malaria.

Malaria can bring about the inhibition of certain liver functions even in the absence of normal clinical signs of hepatic insufficiency. While normal liver functions may be restored after termination of the malarial attack, long continued low-grade malarial infection can cause permanent liver damage (Maegraith, 1948). Liver function has been studied in adults suffering from malaria and in experimental animals. Most studies on liver function have been on *Plasmodium falciparum* malaria, and hepatic dysfunction in *Plasmodium vivax* malaria has received little attention.

Material and methods

Children attending the outpatient department and those admitted to paediatric wards of this hospital in whom a diagnosis of malaria was confirmed by the presence of malarial parasite in the blood were studied. A detailed history was taken and a clinical examination given and then the following investigations were undertaken: serum bilirubin, serum aspartate transaminase (serum AST; SGOT) and alanine transaminase (serum ALT; SGPT), and alkaline phosphatase. Urine was examined for urobilinogen, bile salts, and bile pigments. Children with jaundice were further investigated for red blood cell morphology, reticulocyte count, and Coombs's test.

Observations. 80 children from one month to 3 years of age were studied. *P. vivax* was causative in all. Fever was the chief presenting complaint. Clinically, splenomegaly was present in 83% and hepatomegaly in 68% of cases. Jaundice was observed in only 8·7% of cases; all the jaundiced patients had hepatomegaly.

Out of 54 cases *with hepatomegaly* (group 1) AST was increased in 69%, ALT in 37%, and alkaline phosphatase levels were high in 50%. In 26 cases *without hepatomegaly* (group 2), 65% had increased levels of AST, 38% increased ALT, and 38% had increased alkaline phosphatase levels (Table 1).

Serum bilirubin was increased in 7 cases in group 1. Jaundice in these cases seemed to be hepatocellular in 3, haemolytic in 2, and obstructive in 2 (Table 2).

Urine examination was essentially normal in all except one patient whose urine contained bilirubin (Table 2).

Follow-up showed that 6 weeks after the malarial attack, liver enlargement had diminished, jaundice

Table 1 *Serum enzyme levels*

Investigation	*Group 1 (with hepatomegaly)*		*Group 2 (without hepatomegaly)*	
	Patients with higher levels	*Mean ± SD (U/100 ml serum)*	*Patients with higher levels*	*Mean ± SD (U/100 ml serum)*
AST	37	422·8±80·6	17	144·7±30·2
ALT	21	315·5±60·4	10	102·5±26·5
Alkaline phosphatase	27	25·5*±4·6	10	20·2*±3·8

*KA units.

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Table 2 *Liver function tests in patients with jaundice*

Case no.	*Serum bilirubin (mg/100 ml)*		*Urine*	*AST (U/100 ml)*	*ALT (U/100 ml)*	*Alkaline phosphatase (KA units/100 ml)*	*Evidence of haemolysis*	*Type of jaundice*
	Direct	*Indirect*						
1	1·0	3·2	Normal	28	30	40	+	Haemolytic
2	1·2	5·8	Normal	40	35	28	+	Haemolytic
3	2·0	1·2	Normal	240	190	15	0	Hepatocellular
4	2·2	3·0	Normal	320	280	15	0	Hepatocellular
5	11·8	3·4	Bilirubin	55	45	60	0	Obstructive
6	8·0	2·5	Normal	60	35	45	0	Obstructive
7	4·0	2·4	Normal	160	95	20	0	Hepatocellular

had disappeared, and serum enzymes and bilirubin levels had returned to normal in all cases.

Discussion

Symptoms of disturbed liver function may appear during the course of all forms of malaria (Kern and Norris, 1944), the more serious disturbances being reported in *P. falciparum* infection. The pathogenesis of hepatic dysfunction in malaria is not understood and is probably multifactoral. Liver functions in malaria were studied as early as 1923 by MacCormac and Dodds, who observed an increase in urinary urobilin and urobilinogen, and similar observations were later made by Wallace and Diamond (1925), and Fredricks and Hoffbauer (1945). Increased excretion of urobilin and reduction in excretion of azorubin-S was also noted in *acute* malaria (Maegraith, 1948). Russel (1952) found reduction in total plasma proteins and albumin fraction. Serum α_1-globulin may rise and α_2-globulin fall (Tella and Maegraith, 1965). Serum fibrinogen increases in many cases (Devakul *et al.*, 1966). Increase in plasma bilirubin (Woodruff, 1974), serum glutamic oxalacetic, and pyruvic transaminases (Sadun *et al.*, 1966; Deller *et al.*, 1967) have also been reported. Laevulose tolerance tests performed on malarial patients have suggested hepatic dysfunction (Sinton and Hughes, 1924). Lippincott *et al.* (1945) carried out liver function tests in cases of *chronic* relapsing *P. vivax* malaria and found transient derangement of liver functions in some cases.

In the present study AST and ALT levels were found to be increased in most patients (Table 1), consistent with the observations of Deller *et al.* (1967). Mean levels of AST were higher than ALT although a greater increase in ALT than AST was reported by Sadun *et al.* (1966). AST was increased in 69% cases in group 1, and it is interesting that almost the same percentages of cases (65%) in group 2 also had higher levels of AST. Similar observations were made with ALT levels in the two groups (Table 1). However, within the two groups the levels of these enzymes were higher in the group with hepatomegaly. In half the cases in group 1 alkaline phosphatase levels were increased compared with 38% of cases in group 2 (Table 1) and in these patients the levels of AST and ALT were also raised.

Of 54 patients with disordered liver functions, in 35 the nutritional status was between the 25th and 50th centiles, 16 between the 3rd and 25th centiles, and only 3 cases were below the 3rd centile of Harvard standards. To what extent the nutritional status of these children affected their hepatic function is difficult to know, but as only 6% of cases had severe malnutrition the hepatic dysfunction can be attributed to the acute malaria.

We conclude that mild and transient hepatic dysfunction with increased levels of serum enzymes is a common feature of an acute attack of malaria, with or without hepatomegaly. Jaundice, although an uncommon feature, is associated with more severe hepatocellular damage, while obstructive jaundice seems to imply a more severe hepatic dysfunction.

We are grateful to the Medical Superintendent of Safdarjang Hospital for permitting this study.

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The following articles will appear in future issues of this journal:

A better deal for newborns with congenital heart disease. *F. Macartney.*

The recognition and management of children with increased lead absorption. *J. J. Chisolm and D. Barltrop.*

Structural heart disease in the newborn. Changing profile: comparison of 1975 and 1965. *T. Izukawa, H. C. Mulholland, R. D. Rowe, D. H. Cook, K. R. Bloom, G. A. Trusler, W. G. Williams, and G. W. Chance.*

Dosage schedule for intravenous aminophylline in apnoea of prematurity, based on pharmacokinetic studies. *R. A. K. Jones and E. Baillie.*

Continuing need for mineralocorticoid therapy in salt-losing congenital adrenal hyperplasia. *I. A. Hughes, A. Wilton, C. A. Lole, and O. P. Gray.*

Creatine phosphokinase levels in the newborn and their use in screening for Duchenne muscular dystrophy. *L. M. Drummond.*

Pathogenesis of oxytocin-induced neonatal hyperbilirubinaemia. *S. Singhi and M. Singh.*

Intrapartum sensitisation of human infants to the Rhesus-D antigen. *C. M. Stern.*

Archives of Disease in Childhood, 1979, **54**, 142–151

Short reports

Familial occurrence of omphalocele suggesting sex-linked inheritance

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SUMMARY A family is described in which 4 males in two generations had omphalocele. There was no case of omphalocele in any of the women. It is suggested that the mode of inheritance could be a sex-linked recessive trait.

The occurrence of omphalocele in siblings is rare (McKeown *et al.*, 1953; Irving, 1967; Rothemberg and Barnet, 1974; Rott and Truckenbrodt, 1974) and there is only one report of the presence of this malformation in two generations of a family (Osuna and Lindham, 1976). We report a family in which 4 cases of omphalocele occurred in two generations. Only males were affected, suggesting a sex-linked mode of inheritance.

Case reports

Case 1. (Figure). A male term infant was born to an 18-year-old primigravida, labour was induced because of hypertension. The infant, who weighed 3490 g, had an omphalocele of 4·5 cm in diameter and the sac contained liver and small intestines. A primary closure was done at age 8 hours. He needed to be digitalised for congestive cardiac failure due to a ventricular septal defect which has since closed spontaneously. He did not have macroglossia nor did he develop hypoglycaemia. He is now 36 months old and has developed normally.

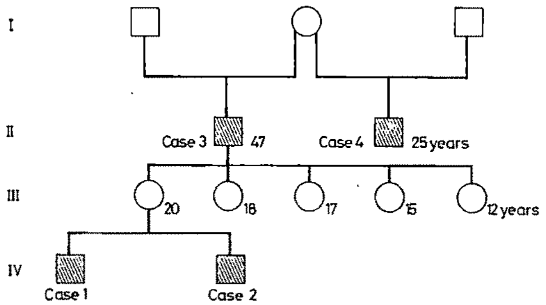

Figure *Family tree showing distribution of omphalocele in male siblings only.*

Case 2. A younger brother of Case 1, was born after a gestation of 40 weeks. The pregnancy was complicated by hydramnios, but labour and delivery were normal. The baby, who weighed 3870 g, had an omphalocele 4 cm in diameter. The sac contained liver and small intestines. Primary closure was performed at age 8 hours and the child had an uneventful postoperative course. There was no evidence of hypoglycaemia. He was discharged from the hospital on the 9th day. Follow-up to age 12 months shows normal development and there is no evidence of any other congenital abnormality.

Family cases. The maternal grandfather (Case 3) of Cases 1 and 2 had had an omphalocele at birth for which surgical closure had been needed. He had no other abnormality. His step brother (Case 4), who was born after his mother remarried, also had an omphalocele at birth for which surgical closure had been needed. There were no other siblings in that generation.

Discussion

Omphalocele is caused by a defect in the development of the abdominal wall. Physiological herniation of the intestines into the extra embryonic coelom of the cord occurs between the 6th and 11th week of embryonic life. Failure of the intestines to re-enter the abdominal cavity results in an omphalocele.

McKeown *et al.* (1953) reported the incidence of omphalocele as 1:3200 in Birmingham, and Soper and Green (1961) reported the incidence as 1:3800 in Ohio.

Omphalocele sometimes occurs in chromosomal aberration as part of the trisomy 13 and 18 syndromes, but its mode of inheritance as a single defect is not known.

Osuna and Lindham (1976) reported a family in which the condition was present in two generations (3 females and one male) suggesting the possibility that omphalocele could be inherited. In the present family omphalocele occurred only in male children and both male siblings of the 2nd generation were affected. All the children in the 3rd generation were female and none had omphalocele. Both male siblings in the 4th generation had omphalocele.

The distribution of the defect in this family suggests an X-linked recessive inheritance with the males being affected and the females acting as carriers.

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Nonaccidental poisoning in childhood

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SUMMARY A boy aged 7 years 10 months was admitted to hospital on several occasions in an unconscious state with twitching and apnoeic episodes. Initial investigations failed to show a specific cause. During his time in hospital he had recurrent episodes of loss of consciousness and, on the last occasion, hypotension and ventricular tachycardia. A diagnosis of imipramine poisoning was established by the presence of imipramine in stomach washings and blood. The drug was being given to the child, both at home and in hospital, by his mother. The possibility of nonaccidental poisoning must be considered if there is no obvious cause for a child's illness. In this case the mother responded to psychiatric treatment.

The syndrome of child abuse incorporates a wide range of features including nutritional and emotional deprivation and violence. However, reports of nonaccidental poisoning are relatively rare. Meadow (1977) and Rogers *et al.* (1976) stated that occasionally parents may assault their children by administering a drug overdose. We describe the case of a child who was systematically and deliberately given toxic doses of a drug for a period of 2 months before the cause could be proved.

Case history

A boy aged 7 years 10 months was admitted to Scartho Road Hospital, Grimsby, in an unconscious state. He was twitching and had apnoeic episodes. Investigations at that time, including a full blood count, blood urea and electrolytes, and cerebrospinal fluid, were normal. He recovered consciousness over a period of 48 hours and was well on discharge from hospital 14 days later. At that time his parents, in response to specific questioning, denied that there was any possibility of the child having had an overdose of drugs. The inquiry was specific as the patient had been treated for enuresis in 1974, 1976 and, in the month before this illness, with amitriptyline. After discharge he vomited each day and was readmitted to hospital in a drowsy but rousable state one month later. He was treated with intravenous fluids for mild dehydration and his level of consciousness gradually improved. During the next week while in hospital, he had episodes of drowsiness and disorientation associated with bizarre jerking of eyes and limbs. These episodes occurred mainly in the evenings after his mother had visited him. He was referred to Dr J. Lorber at the Sheffield Children's Hospital for further assessment. At the time of transfer he was drowsy and had writhing movements of the limbs. There were no other neurological abnormalities. Again, his parents specifically denied that he had had any access to toxic drugs. He fully recovered within 12 hours of admission, and therefore no further investigations were carried out.

He was discharged but readmitted 12 days later because of gradual loss of consciousness during the previous 24 hours. He was unconscious, had myoclonic twitching of his limbs, nystagmus, hypotension,

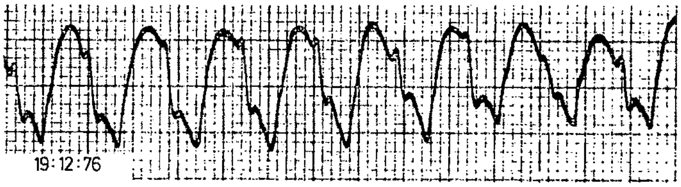

Fig. 1 *ECG before treatment.*

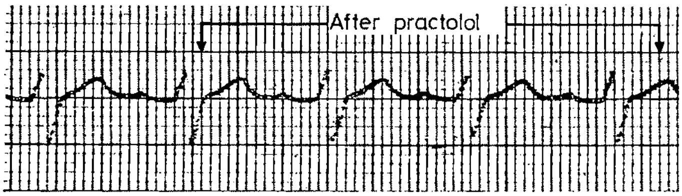

Fig. 2 *ECG after treament with practolol and lignocaine.*

and ventricular tachycardia (Fig. 1). In consultation with the general physician (D.B.C.) he was treated with synchronised DC currents 75, 100, and 200 joules without effect. The ECG reverted to normal (Fig. 2) after IV practolol and lignocaine. Treatment with IV lignocaine was continued for 24 hours. He gradually regained consciousness and was symptom-free within 3 days. Blood samples taken at the time of admission did not contain amitriptyline. 48 hours after he had become symptom-free he had further symptoms and on this occasion blood and stomach washings showed imipramine, which is the active constituent of Tofranil, to be present, together with its major metabolite desipramine, in the following amounts: stomach wash: 0·5 mg/100ml; blood: 0·15 mg/100 ml. Such a blood level could only be reached by the ingestion of several 25 mg Tofranil tablets.

On this occasion the mother admitted that she had been giving large doses of imipramine to her son, both at home and in hospital. The drug had been prescribed for her own use.

Discussion

The child's mother was found on psychiatric assessment to have a character disorder with superimposed depression. A baby girl had died suddenly just before our patient was conceived and this appeared to be the trigger factor which culminated in the administration of drugs to our patient. This projection and defence against the reality of the boy not being her 'dead daughter' was thought to lead to her giving drugs to the boy to reinforce his feminine and infantile traits and, failing this, to ensure his death just as her baby girl had died. The mother was confined to a psychiatric hospital after the incident and her depressive symptoms responded to treatment. The father was supportive throughout the period of his wife's hospital treatment. The boy returned home and after a long period of psychotherapy the mother is now also at home and under close supervision.

Nonaccidental poisoning is an unusual but potentially lethal form of child abuse. The patient may present with a variety of symptoms depending on the drug, and an awareness of the possibility of poisoning in any patient with unexplained symptoms is vital. It is not always possible, as it was in this case, to ascertain why such deliberate poisoning may occur.

We thank Dr J. Lorber for his permission to report on this patient, Dr D. B. Carron for successfully treating the child's ventricular tachycardia, Mrs P. Johnson, clinical psychologist, and the Forensic Science Laboratory at Harrogate for the estimation of amitriptyline and imipramine.

Addendum

Since this case was reported we have seen another child to whom the mother had given a drug at home and in hospital, and a solution to the problem evaded us for some time.

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Quantitation of digital clubbing by shadowgram technique

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SUMMARY Finger clubbing was quantified from the magnified silhouette of the right index finger in controls and patients with clubbing, using a simple shadowgram technique. There was good correlation between clinical assessment and measurement of both the profile angle and the hyponychial angle. The hyponychial angle appeared to be a more accurate indicator of clubbing than the profile angle.

Finger clubbing was first recognised during the time of Hippocrates as an important sign of underlying pulmonary disease (*Lancet*, 1975). Since then it has been observed in many cardiac, hepatic, and intestinal disorders as well as in some other diseases, but there have been few attempts to quantitate the degree of abnormality (Regan *et al.*, 1967; Bentley *et al.*, 1976). Clinical assessment is subjective and can be difficult in mild cases. A technique that established the presence and extent of clubbing, particularly in confusing clinical situations, and which could be used to follow its course would be valuable.

Using digital cast technique, Regan *et al.* (1967) found that the best parameter of clubbing was the hyponychial angle. Bentley *et al.* (1976) measured the magnified silhouette of the index finger and also found the hyponychial angle a better indicator than the profile angle. We report a simple method of quantifying clubbing using a shadowgram technique.

Materials and methods

A standard overhead projector (3M Company) was used to project the magnified silhouette of the distal segment of the right index finger on to a screen. The finger was positioned and supported by an assistant and the image obtained was then outlined on paper. The profile and hyponychial angles were then constructed as shown in the Figure.

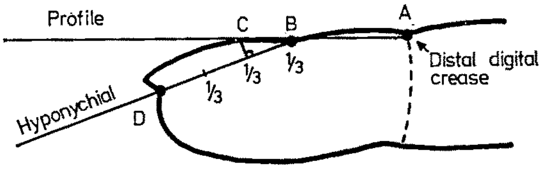

Figure *Profile and hyponychial angles.*
A = distal digital crease. B = datum point (cuticle). C = point at which a perpendicular from one-third of the distance BD meets the nail. D = hyponychium (thickened stratum corneum of epidermis lying under the free edge of nail). ABC = profile angle. ABD = hyponychial angle. (From Bentley *et al.*, 1976).

Those studied were: (a) 20 control subjects (10 boys and 10 girls) aged 1–12 years (mean 6·7 ± 3·4 SD); (b) 19 patients with clinical clubbing (obliteration of the angle of the base of the nail and abnormal fluctuation) (9 boys and 10 girls) aged 2–12 years (mean 6·9 ± 2·7 SD). The patients, comprised 10 with thalassaemia major, 5 with congenital cyanotic heart disease, 3 with malabsorption syndrome, and one with bronchiectasis. 16 of them had clubbing of all the fingers, while 3 had clubbing of the middle and/or ring finger but not of the index finger.

Results

The results are summarised in the Table. There were no significant differences between the sexes and mean ages of control subjects and patients (P>0·9; P>0·8).

Profile angle. The mean profile angle of control subjects and patients was 171·4° (SD ±5·6°, range 154–176°) and 182·9° (SD ±4·7°, range 171–189°) respectively. There were significant differences between the mean profile angles of the two groups (P<0·001).

The profile angle exceeded the normal range (171–189°) in 18 of the 19 patients and it was normal in one patient who had only slight clinical clubbing.

Hyponychial angle. The mean hyponychial angle of the right index finger of control subjects and patients

Table *Profile and hyponychial angles of the right index finger of control subjects and patients with clinical clubbing*

	Controls (*n* = *20*)	*Patients* (*n* = *19*)	*t value*	*P*
Age (years)				
Mean ± SD	6·7±3·4	6·9±2·7		
Range	1–12	2–12	0·2	0·9>P>0·8
Profile angle °				
Mean ± SD	171·4±5·5	182·9±4·7		
Range	154–176	171–189	7·0	<0·001
Hyponychial angle °				
Mean ± SD	180·7±5·2	194·5±7·5		
Range	165–189	178–205	6·7	<0·001

was 180·7° (SD ±5·2°, range 165–189°) and 194·5° (SD ±7·5°, range 178–205°) respectively. There were highly significant differences between the mean hyponychial angles of the two groups ($P < 0 \cdot 001$).

16 of the 19 patients had profile angles which exceeded the normal range, while 3 with clinical clubbing of the middle and/or ring finger, but not of the index finger, had normal angles. There was good correlation between the clinical diagnosis of clubbing and assessment by the shadowgram.

Discussion

Clinical assessment of finger clubbing is subjective and unreliable (Pyke, 1954; Carroll, 1972) but it is very useful as an indicator of underlying disease. The shadowgraph is a cheap and simple technique which allows serial measurements of the profile and hyponychial angles to be made speedily and without discomfort. There is excellent correlation between the clinical diagnosis of clubbing and assessment by this technique. The hyponychial angle appears to correlate more closely with the clinical diagnosis than the profile angle, as was found by Regan *et al.* (1967) and Bentley *et al.* (1976).

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Fatal bleeding from gastric ulceration during first day of life—possible association with social stress

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SUMMARY Death from haemorrhage is described in a 21-hour-old baby boy with acute gastric ulceration. Particular note is made of the very high level of psychosocial maternal stress during the last trimester of pregnancy. A causal relationship of this stress and the peptic ulceration is suggested, with gastrin as the mediator.

A 17-year-old primigravida was admitted in labour after an uncomplicated pregnancy and monitored cardio-tocographically without causing concern. The first stage of labour lasted 5 hours and the second 20 minutes, producing a healthy baby boy at term, weighing 2·73 kg, by a spontaneous normal vaginal delivery. The Apgar score was 4 at one minute and 8 at five minutes. No special resuscitative procedures were needed, no nasogastric tube was passed, and vitamin K 1 mg was administered intramuscularly.

The baby had normal infant care alongside its mother, taking 5% dextrose solution eagerly by bottle until, at age 20 hours, fresh blood was vomited and shown by Apt's test to be of infant origin. Clinical examination then showed a vigorous baby with no purpura, bruising, or haemangiomata. There was no family history of bleeding disorder, and no aspirin or similar drugs had been administered to the mother at the relevant time. The mother was in good health. A venous blood sample on admission at 20 hours showed the baby to have a haemoglobin of 14·2 g/dl, a platelet count of $160 \times 10^9/l$ (160 000/mm^3), and no abnormality in the prothrombin, partial thromboplastin, or thrombin times. A similar coagulation screen of the mother's blood was also normal.

During the next half-hour further fresh blood was vomited repeatedly, resulting in a critical degree of shock with apathy and loss of awareness. A catheter introduced into the inferior vena cava via the umbilical vein recorded a low central venous pressure and 75 ml of O-negative whole blood was transfused rapidly with only fleeting benefit. Death supervened at 21 hours, only one hour after the first haematemesis.

Necropsy showed the source of bleeding to be 3 areas of gastric ulceration: 2 on the posterior wall and one on the greater curvature (Figure). Histological examination showed that they were of the acute peptic

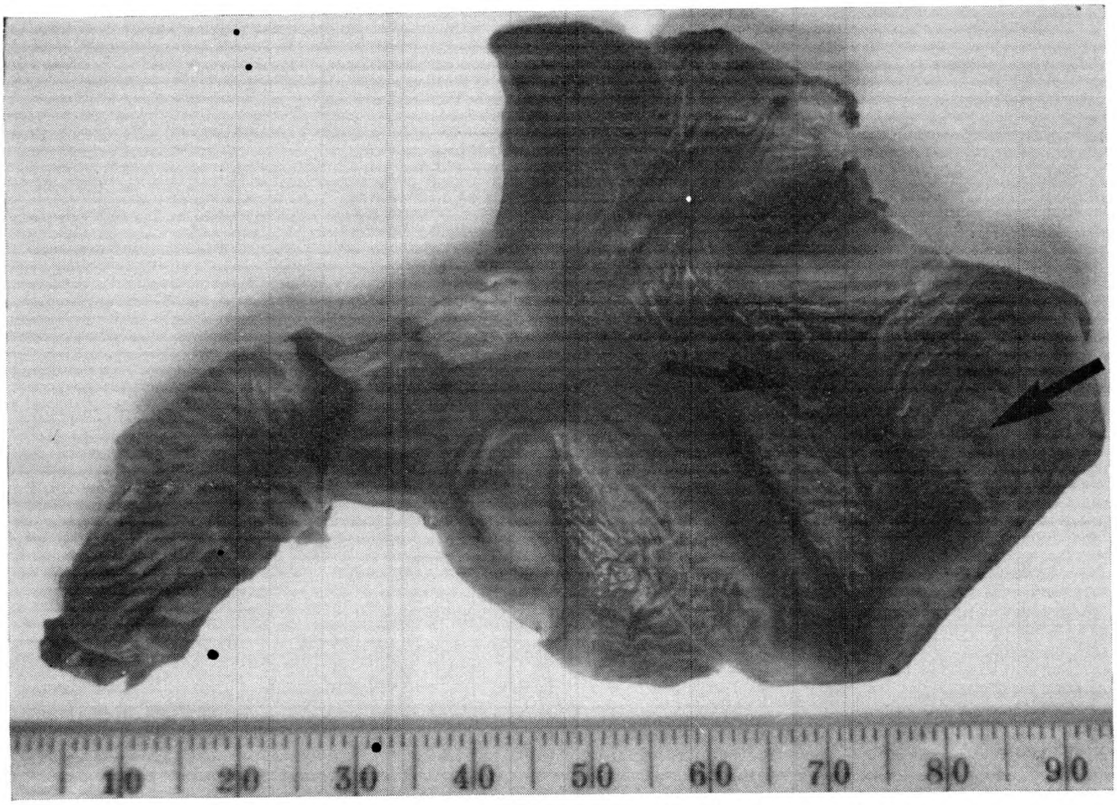

Figure *Two peptic ulcers on the posterior gastric wall (note remnant blood clot in upper ulcer).*

type with endarteritic changes in the smaller, most distal, ulcer.

After this tragic death a discreet social inquiry found that the pregnancy, and particularly the last trimester, had been exceptionally stressful and unhappy. At the time of conception the mother was only 16, unmarried, and working in a factory as a hosiery examiner. She married the equally young father to comply with parental wishes, but lived with him for only 2 weeks before returning to her parents' home to escape from drunken physical assaults. Subsequently her husband made frequent visits to her parents' home in ill-conceived attempts at reconciliation, causing great distress, panic, and revulsion. One such visit shortly before labour began culminated in a brick being thrown at her through the living-room window and the intervention of the police.

Comment

The occurrence of peptic ulceration in the newborn infant, particularly in boys, has often been described. Presentation is usually with haematemesis or perforation (Bird *et al.*, 1941; Smith, 1975). We know that stress increases the incidence of peptic ulceration in adults (Rose, 1978) and the possibility exists that greatly increased maternal stress late in the pregnancy may have a similar association with gastric ulceration in the newly born—presumably mediated by a maternal hormone crossing the placenta.

When gastrin is administered to the experimental dog late in pregnancy there is an increased incidence of pyloric stenosis, in some cases associated with pyloro-duodenal ulceration in the offspring (Dodge, 1970; Karim *et al.*, 1974). Dodge (1972) and Revill and Dodge (1978) drew attention to the higher incidence of maternal stress in the latter part of pregnancy in babies with pyloric stenosis and suggested that gastrin is the biochemical mediator.

We believe our patient to be the first in whom gastric ulceration with bleeding in the first day of life has been tentatively identified with maternal stress as cause and effect. It is possible that in this case gastrin was the biochemical mediator of the stress and the cause of gastric ulceration.

Conclusion

A careful social history may be particularly relevant in high gastrointestinal bleeding or perforation in the early newborn period. Conversely, such pregnancies should be regarded as particularly at risk and managed accordingly.

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Hepatomegaly due to self-induced hyperinsulinism

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SUMMARY Repeated hypoglycaemic attacks, associated with transient hepatomegaly, in a 12-year-old insulin-dependent diabetic girl continued despite reduction in dose and, later, complete discontinuance of insulin. The attacks ceased while she was in hospital, necessitating reinstitution of insulin. The hepatomegaly resolved when surreptitious additional insulin injections were discovered and stopped. Hepatomegaly in diabetics should arouse suspicion of over dosage with insulin.

Hepatomegaly associated with diabetic hypoglycaemia was well known before long-acting insulin became available (Madison, 1969), but it has seldom been encountered recently (Rosenbloom and Giordano, 1977). We present a 12-year-old insulin-dependent diabetic with transient hepatomegaly associated with hypoglycaemia induced by surreptitious additional insulin injections, and discuss the role of over dosage with insulin in inducing hepatomegaly.

Case report

We have followed-up a 12-year-old girl since age 5 when insulin-dependent diabetes was diagnosed and treatment initiated. For 7 years control was good, but then frequent hypoglycaemic attacks of moderate severity were reported. The hypoglycaemic attacks persisted despite reduction in insulin dose and, later, its complete discontinuance. Marked hepatomegaly was noted, and the girl was admitted for investigation.

She was then a lean, normotensive, healthy looking child with a firm, tender liver palpable 12 cm below the costal margin. SGOT 138 IU/ml (normal <40), LDH 156 IU/ml (normal <235), alkaline phosphatase 181 IU/ml (normal for age), acid phosphatase 1·5 U/ml (normal 0–1), bromosulphalein retention 2·4% after 45 min, serum ammonia 57 μg/100 ml (normal <85), antitrypsin 88 mg/100 ml (0·88 g/l) α-fetoprotein negative; normal bilirubin, electrolytes, and copper ceruloplasmin. Australian antigen tests, endocrinological studies including evaluation of pituitary and adrenal, and haematological study, including bone marrow aspiration, were all normal. Scan showed diffuse liver enlargement and a normal spleen (Fig. 1a).

After 3 days without treatment, the fasting serum insulin was 5·2 μU/ml. Because of hyperglycaemia (up to 405 mg/dl) and glycosuria (up to 4%), the insulin was restarted. The hypoglycaemic attacks then ceased, the liver size decreased to 6 cm below the costal margin, and she was discharged.

After 5 months of good control in which only the edge of the liver remained palpable (Fig. 1b) the hypoglycaemia and hepatomegaly recurred. Because of the history and laboratory findings, we suspected overinsulinism. The mother then discovered that the girl surreptitiously injected additional insulin, probably to attract notice by provoking hypoglycaemic spells.

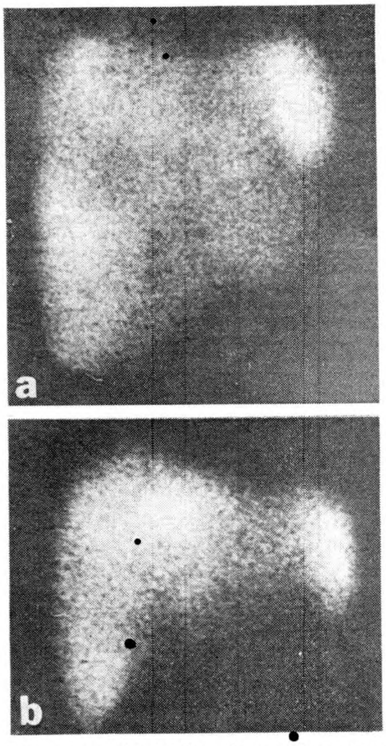

Figure *Liver scan.* (*a*) *Diffuse liver enlargement during overinsulinism;* (*b*) *Decreased liver size after adjustment of insulin dose.*

We insisted that the extra insulin injections be stopped and referred the girl to a psychologist. The hypoglycaemic episodes then disappeared and the hepatomegaly resolved within a few weeks.

Discussion

After excluding diseases associated with hepatomegaly, the diagnosis lay between uncontrolled diabetes and over dosage with insulin. The long periods of good control and disappearance of hypoglycaemia during observation in hospital favoured the latter.

Rosenbloom and Giordano (1977) reviewing overtreatment in diabetic children noted findings similar to those of our patient. Hepatomegaly associated with protracted hypoglycaemia was noted before the availability of long-acting insulin, mainly among poorly controlled juvenile diabetics treated with daily, multiple injections of regular insulin (Mandell and Berenberg, 1974). The hepatomegaly of hyperinsulinism is thought to be secondary to accumulation of glycogen in the liver by inhibition of cyclic-AMP synthesis (Bishop *et al.*, 1965; Mortimore *et al.*, 1967; Davidson and Berliner, 1974; Dershewitz *et al.*, 1976). Insulin is known to affect hepatic glucose metabolism directly (Madison, 1969) by increasing the uptake and decreasing the output (Steele *et al.*, 1965). Liver glucose output is largely determined by opposing effects of insulin and glucagon (Jefferson *et al.*, 1968). Glucagon increases the hepatic cyclic-AMP, thus stimulating glycogenolysis and gluconeogenesis (Robison *et al.*, 1971). Insulin opposes this effect by inhibiting the synthesis and increasing the degradation of cyclic-AMP (Jefferson *et al.*, 1968), thus leading to increased glycogen storage.

The excessive insulin taken by our patient undoubtedly disturbed the balance between insulin and glucagon, leading to increased glycogen storage in the liver which presumably was responsible for the hepatomegaly. Stopping the insulin overdose, enabled the glucagon to increase the synthesis of cyclic-AMP, thus inducing gycogenolysis and resolution of the hepatomegaly.

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Phenothiazine-induced dystonia associated with an increase in serum creatine phosphokinase

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SUMMARY A transient but considerable rise in serum creatine phosphokinase (CPK) levels occurred in six boys aged between 8 and 11 years and suffering from phenothiazine-induced dystonia. In one boy (Case 4), after the CPK level had returned to normal after withdrawal of the drug, its reintroduction orally at lower dosage caused a slight increase in the level of CPK in the absence of any recurrence of the dystonia.

Muscle dystonia associated with administration of certain phenothiazine derivatives is well known (Goldsmith, 1959; Ayd, 1961). Laboratory investigations in such patients have been normal. In a survey of serum creatine phosphokinase (CPK) levels in Chinese children, it was noticed that there was a transient increase in CPK levels in some children who suffered drug-induced dystonia.

Material and methods

Six Chinese boys aged between 8 and 11 years were admitted for dystonia into this hospital. Four had received phenothiazine derivatives orally. A single IM injection of prochlorperazine had been given in 2 other boys. None had a disease known to be associated with raised levels of CPK. Apart from the 2 boys who each had received one IM injection of prochlorperazine, none had had any medical treatment known to cause an increase in CPK. Their clinical details are given in the Table. Between 24 and 48 hours after oral or IM administration of the drug, the child generally developed painful spasms of facial, neck, and sometimes limb muscles. The head and sometimes the eyes were deviated involuntarily to one direction. The mouth was open, or spasmodic attacks of trismus occurred. One or more extremities, and at times the whole body, might be held spasmodically in a bizarre posture. The child was invariably conscious but could not speak as a result of muscle spasms.

IV diphenhydramine was given to 4 boys after being in hospital; the other 2 received no treatment. Dystonia subsided within 36 hours in all 6 boys, but pain in affected muscles persisted for 2 to 7 days.

Serum was collected immediately after admission and then serially. CPK was assayed immediately after collection or after storage in dark containers at −20°C for not more than 5 days. A colorimetric method using Sigma kit 661-PB was used. The normal range with this method in Chinese boys of this age group is 2–17 Sigma units/ml.

Table *Clinical details and serum CPK levels*

Age (years)	*Drug responsible*	*Dystonia*		*Features*	*Duration of muscle pain (days)*	*Peak serum CPK level* (Sigma units/ml)*	*Duration of raised serum CPK*
		Onset (hours)	*Duration (hours)*				
9½	Prochlorperazine 5 mg oral × 2 for vomiting	Within 24	24	Torsion head and neck	4	104	Days 2–6
11	Perphenazine 2 mg oral × 3 for vomiting	Within 24	36	Torsion head and neck	2	84	Days 2–5
9	Haloperidol 0·5 mg oral for behavioural problems	Within 24	48	Torsion head, oculogyric crisis, mouth open, salivation, sweating	3	30	Days 2–4
8	Haloperidol 1 mg oral × 3 for behavioural problems	Within 36	24	Trismus, torsion head and neck	7	74	Days 2–6 11 (see text)
9½	Prochlorperazine 12·5 mg IM for vomiting	Within 24	24	Torsion head and neck, rigid limbs	2	135	Days 2–3
11	Prochlorperazine 12·5 mg IM for vomiting	Within 24	24	Oculogyric crisis torsion head and neck	2	97	Days 1–3

*Normal range 2–17 Sigma units/ml.

Results

In all 6 boys, serum CPK was abnormally high, reaching a peak level between 2 and 4 days after the onset of dystonia. Thereafter the levels dropped to normal within a week. The peak levels reached ranged from 30 to 135 Sigma units/ml.

In one 8-year-old boy (Case 4), in whom dystonia had been induced by three oral 1 mg doses of haloperidol given within a day (for psychiatric symptoms), the peak CPK level was 74 Sigma units/ml. After withdrawal of haloperidol, the level fell to 9 Sigma units/ml in a week. Three days after reintroducing the drug at 0·5 mg twice a day, his CPK level rose to 19 Sigma units/ml, but without any recurrence either of muscle pain or dystonia.

Discussion

Raised levels of serum CPK have been known to be associated with active progressive muscular dystrophy, acute polymyositis, periodic paralysis, repeated intramuscular infections, strenuous exercise, myocardial infarction, and cardiac catheterisation, and also with the immediate newborn period. Although increased levels of CPK have been reported in patients with Wilson's disease who had marked rigidity (Okinaka *et al.*, 1964), its increase in patients suffering from drug-induced dystonia was not reported. With severe muscle dystonia, this enzyme may perhaps be released into the circulation. Previous reports on phenothiazine-induced dystonia found no correlation between the dosage or route of administration of the drug, and the occurrence and severity of dystonia (Goldsmith, 1959). It is notable however that in our Case 4 the CPK level rose again on reintroducing the drug at a lower dosage but did not cause dystonia or muscle pain. This raises the possibility that the offending drug at a lower dosage may lead to subclinical disturbances of muscle function.

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Paediatric Pathology Society

Proceedings of the Twenty-fourth Annual Meeting

The meeting was held on 21–23 September 1978 at the Bristol Maternity Hospital. Lack of space precludes the publication of summaries of all the unusually large number of papers read.*

Morbid anatomists' role in a diagnostic amniocentesis service. D. I. Rushton. Department of Pathology, Birmingham Maternity Hospital, Birmingham.

The role of the morbid anatomist in a diagnostic amniocentesis service is primarily (a) to assess the wastage due to the procedure and (b) to confirm antenatal diagnoses resulting from examination of amniotic fluids. The description of the fetal manifestations of disease is also important. The inadequacies of current services and the dangers of failure of consideration of normal patterns of pregnancy wastage at the appropriate gestation are stressed. It is suggested that data may give a falsely low estimate of fetal wastage attributed to amniocentesis.

Pathology of congenital disclocation of the hip. P. M. Dunn. Department of Child Health, Southmead Hospital, Bristol.

During the period 1961–75 50 hips considered on clinical examination to be either dislocatable or dislocated at birth were examined at necropsy. All the infants died during the neonatal period, most of them within 3 days of birth. Gestational ages ranged from 27 to 44 weeks. 16 of 33 infants had presented by the breech at delivery. Infants with obvious or suspected neuromuscular disease were not included. Dissection confirmed abnormality in each case. Pathology ranged from instability of the fibrocartilaginous labrum with increased joint laxity in the dislocatable hips to full dislocation with inturned limbus compressed between the outlying head of femur and true acetabulum. One hip was dysplastic without being dislocated. No case of 'fixed', stable dislocation was encountered. The degree of abnormality often varied between the two hips, and every combination from normality to mild or severe change was found. At least 50 hips considered normal on clinical examination were dissected and normality was confirmed. These findings, and the results of epidemiological studies, suggest that congenital dislocation of the hip may be defined as a deformity of the hip joint, arising during fetal life and present at birth, in which the head of the femur is, or may be, partially or completely dislocated from the acetabulum. The findings also show that hip disease is common at birth and may reliably be detected by clinical examination.

Tyrosinaemia—an atypical case. J. T. Ireland and C. Davidson. Alder Hey Children's Hospital, Liverpool.

Toxicological screening in cases of sudden infant death syndrome. C. N. Chapman and N. J. Brown. Bristol Maternity Hospital, Bristol.

Using an analytical scheme designed to detect drugs most likely to be encountered, a screening programme was initiated. It was thought this might show the presence of substances which, if not the prime cause of death, might have contributed thereto. Samples of stomach contents and liver were examined from 47 cases, with the following results: no drugs detected —31; benzodiazepines—5; phenobarbitone—3; unidentified acid compound—1; unidentified basic compound—7. The unidentified compounds are not necessarily drugs; they could well be post-mortem decomposition products. The amounts of material detected were very small. There was no case of anything that might be called an overt example of poisoning.

Fetal pathology: termination of pregnancy in the second trimester. A. A. M. Gibson. Royal Hospital for Sick Children, Glasgow.

A series of over 150 cases in which the indication for termination of pregnancy was the antenatal diagnosis of fetal malformation.

Differential delay in myelination of vagal fibres—its relation to apnoea of prematurity and the sudden-infant-death syndrome. P. N. Sachis, D. L. Armstrong,

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*Abstracts may be obtained from Dr R. A. Risdon, Secretary, Paediatric Pathology Society, Institute of Pathology, The London Hospital, London E1 1BB.

L. E. Becker, and A. C. Bryan. Departments of Pathology and Respiratory Physiology, The Hospital for Sick Children, Toronto, Canada.

Apnoea is especially common in premature infants, and abnormal control of breathing has been implicated in the sudden-infant-death syndrome (SIDS). Because vagal pulmonary reflexes change with maturation, we studied 'normal' morphological vagal ontogeny and compared this with the morphology in SIDS victims. Total and small myelinated fibres (MF) were sparse in premature infants. In vagi of 'SIDS-age' infants, despite the lower mean postconceptional age, their mean MF total compared with that in SIDS: however, small MF were significantly fewer in SIDS—only slightly more than in the premature. Lack of myelin impairs temporal summation of excitatory postsynaptic potentials and may alter the nature of both afferent and efferent signals. As 1–2 μm is the critical diameter where myelination increases conduction velocity, our findings accord with the reduced neural respiratory control in premature infants and may relate to SIDS.

Histochemical and densitometric study of cartilage in a case of achondrogenesis type II. J. J. van der Harten, G. J. M. Hooghwinkel, and D. Toornvleit. Free University, Amsterdam, The Netherlands.

Asplenia-polysplenia: a comparative study of susceptibility to infection. V. Mahnovski, V. M. Anderson, and A. I. Lipsey. Department of Pathology, Children's Hospital of Los Angeles, California, USA.

Asplenia in the Ivemark syndrome—evidence against primary agenesis. V. M. Anderson and V. Mahnovski. Department of Pathology, Children's Hospital of Los Angeles, California, USA.

Pulmonary and myocardial changes in premature infants after mechanical ventilation. H. Nordgren and A. Petersson. Department of Pathology, University Hospital, Lund, Sweden.

19 premature infants, gestational ages 26–40 weeks, treated with mechanical ventilation were studied at necropsy. A comparison was made between gestational age, weight, time of ventilation, age at death, and microscopical changes in lungs and myocardium. The lung changes were classified according to the criteria suggested by Rosean and the myocardial changes were graded into three groups ranging from oedema to calcification. Three different groups were easily distinguishable. The 1st, ventilated for 1–7 days, showed only minor changes in myocardium and lungs. The 2nd, ventilated for 9–14 days, showed more obvious changes—BPD II–III and slight myocardial fibrosis. The 3rd group, ventilated for 1–6 months, showed severe, apparently irreversible damage—BPD III–IV, and fibrotic scarring of the myocardium; in some cases calcification was observed. The myocardial changes were particularly prominent in the subendocardial zone in the right ventricle. These changes indicate ischaemic damage, and the presence of calcification supports the theory that ischaemic damage leads to an increase of the cellular calcium concentration.

Betamimetics and neonatal lung adaptation. B. Bergman, U. Freyschuss, G. Grossman, T. Hedner, B. Lachmann, and B. Robertson. Department of Paediatric Pathology, Karolinska Institutet, Stockholm, Sweden.

There is now evidence that certain betamimetic agents, administered to the mother or injected into the premature fetus, have a direct influence on the developing lung by stimulating a release of surface active phospholipids in the fetal pulmonary fluid (FPF) and by reducing the water content of the fetal lung. To analyse whether antenatal treatment with a betamimetic agent influences neonatal lung mechanics *in vivo*, we recorded pneumotachogram and oesophagus pressure in premature rabbit neonates, delivered on day 28 of gestation, 3 hours after IM injection of terbutaline (0·1 mg). In recordings made 30 min after birth, we found reduced expiratory resistance in treated animals, but otherwise no difference between experimental neonates and controls. Thus, although administration of beta-stimulants to the premature fetus has a strong influence on the amount and composition of FPF, and although the pressure/volume characteristics of the neonatal lung appear to be improved after such treatment, these effects seem to have only slight influence on lung mechanics during the subsequent phase of neonatal adaptation.

A breakdown of factors present with children found unexpectedly dead. J. L. Emery and P. M. McWeeny. Children's Hospital, Sheffield.

A survey was carried out of the morbid anatomical findings and the clinical history, based largely on a home visit by a social research worker, from a sequential series of about 100 postperinatal deaths in the Sheffield area before March 1976. In most cases there were multiple factors. Necropsy showed that over one-third of the babies had evidence of what was probably subclinical damage to the brain dating from the perinatal period. Many terminal diseases were present, only a few of which would usually be considered adequate causes of death in themselves. There were a few deaths that were probably not due to natural causes but were, at presentation, legally unprovable and indistinguishable from unexplained deaths. Social factors show many features affecting the child that were acting before the child's birth and a variety of defects in the interfaces between the family and the health service, and within the health service itself. The findings give a hint of the features that could well be shown to be variable throughout the country when the findings of the current multicentre study will be completed.

Thymus reaction and its relationship to duration and severity of symptoms in infants. J. W. Keeling, D. Scott, I. Forrest-Hay, and J. Oakley. DHSS Multicentre Post Perinatal Mortality Study.

Hydrops fetalis and diffuse arterial calcification. J. W. Keeling and J. D. Baum. John Radcliffe Maternity Hospital, Oxford.

Critical study of thymic pathology in children with malnutrition infection morbid complex. K. Madi, C. L. Ávila, and A. V. Oliveira. Departamento de Patologia, Universidade Federal do Rio de Janeiro, Brazil.

Malnutrition has been held responsible for a type of thymic hypoplasia common in children from underdeveloped countries. Evidence shows that this hypoplasia is caused by a combination of malnutrition, infection, and stress. Two types of lesion are described: *thymic involution*, where, besides reduction of size and of lymphoid population (which produces blurring of cortico-medullary demarcation) there is cystic dilatation of Hassall's corpuscles; and *atrophy*, where, besides severe weight loss, Hassall's corpuscles are absent or reduced in number and size. There is similar lymphoid hypoplasia in the other organs with rudimentary follicles in the lymph nodes and spleen, and hypocellularity of intestinal lamina propria. The number of cases with absence of Hassall's corpuscles is large enough to discourage the authors from considering them as a primary immunological deficiency. In addition it is argued whether some thymic hypoplasias described as congenital are really the result of a process similar to that seen in our cases.

Vascular changes in the lungs of infants following parenteral lipid nutrition. A. Moragas and A. Ballabriga. Departments of Pathology and Paediatrics, Ciudad Sanitaria de la Seguridad Social and Facultad de Medicina Automoma de Barcelona.

In a necropsy series of 22 infants aged 7–123 days who had received parenteral lipid nutrition from 4 to 27 days, lipid droplets in alveolar capillaries were found in 8 cases (36%), lipoid alveolitis in 3 (14%), and severe changes associated with fat deposition in intrapulmonary arteries from 0·1–0·6 mm diameter in 17 (77%). According to the prevalent type of arterial lesion the cases were classified in stages I to IV (early lesions, acute florid stage, lipophagic stage, and regressive stage) which showed a good correlation with the length of lipid treatment or the lapse of time between the start of treatment and death. All the early cases and 88% of florid acute cases were found in infants treated for up to 8 days. It is suggested that the lesions develop differently in term compared with premature babies, the latter showing a prevalence of acute florid lesions with little lipophagic response. The main factor in the pathogenesis of the lesions is considered to be previous injury to the arterial wall mediated by hypoxia or acidosis. It is assumed that the degree of lipidisation does not depend primarily on the length of lipid treatment, since there is a tendency for this to regress with time. It is not known if a persistent narrowing of pulmonary vessels could be a significant cause of pulmonary hypertension in later life.

Tentorial tears as a problem for the paediatrician. A. J. Barson. Department of Pathology, St Mary's Hospital, Manchester.

40 infants dying from intracranial haemorrhage secondary to tentorial tears between 1967 and 1978 were reviewed. Increased numbers of such deaths have been seen since the establishment of a regional service for the intensive care of the newborn infant. This is because priority for admission has tended to be given to infants with respiratory difficulty which cannot easily be accounted for either by prematurity or gross malformation. Although most of these infants die within 48 hours of birth it is difficult to differentiate them from infants with uncomplicated respiratory distress syndrome in whom the prognosis is much better. Indeed one-quarter of the infants with tentorial tears also had hyaline membrane disease at death, and about one-third had some form of internal congenital malformation. The incidence of tentorial tear is approximately 1 per 1000 births and does not seem to have changed significantly during the last decade. However, the development of intensive care facilities for the newborn with respiratory difficulty has made this a major problem for the neonatologist.

Congenital cystic disease of lung. P. M. Bale. Royal Alexandra Hospital for Children, Sydney, Australia.

44 cases of cystic lungs in children were studied in an attempt to determine (1) how often congenital cystic disease could be clearly distinguished from post-inflammatory pneumatoceles and bronchiectasis, and (2) whether true congenital cystic malformation and adenomatoid malformation were separate entities or variants of the same condition. 22 cases were classed as congenital cystic malformation, 2 as adenomatoid malformation, and one as intrapulmonary bronchogenic cyst. In 16 cases chronic inflammation and fibrosis precluded differentiation of inflammed congenital cystic disease from post-inflammatory pneumatocele, and 3 were intermediate between lobar emphysema and cystic malformation. Cystic and adenomatoid malformations were considered to be similar bronchiolar malformations falling into 2 overlapping clinico-pathological groups: (1) cystic malformation in term infants and children with predominantly cystic lobes and interspersed mature alveoli, and (2) adenomatoid malformation in oedematous stillborn and premature infants with predominantly solid lobes showing more epithelial proliferation and immature terminal airways.

Pancreatic changes in the normal and cystic fibrosis infant. J. R. Imrie, D. G. Fagan, and J. M. Sturgess. The Hospital for Sick Children, Toronto, Canada.

The clinical and pathological diagnosis of cystic fibrosis (CF) in infants, with or without meconium ileus, often proves difficult, and is subjective. To establish objective criteria of the morphological changes, the exocrine pancreas of CF and normal children was analysed by quantitative stereological techniques. In the normal pancreas, the ratio of acinar to connective tissue increases linearly from 32 to 54 weeks' postconceptional age (PCA). In CF, there is a reversed pattern of development: the ratio of acinar to connective tissue decreases linearly and the values are significantly different from the controls after 42 weeks' PCA. Thus lack of acinar developmend and/or degeneration appears similar in all CF patients, with or without a history of meconium ileus. Dilatation of pancreatic ducts and acinar lumina with inspissated secretions results in an increased lumen volume in 83% of CF infants. This change is independent of the acinar and connective tissue variation and indicates that obstruction of ducts is not the only factor responsible for acinar maldevelopment, degeneration, and fibrosis. After analysis of both the acinar to connective tissue ratio and lumen volume, only 2 out of 30 CF infants defied differentiation from normal controls. By quantitative microscopy, we developed the basis for a simple objective diagnostic method for CF by examining the pancreas alone. This may prove valuable in confirming a tentative diagnosis of CF in the absence of clinical proof, and so aid genetic counselling.

Thymus pathology and lymphadenopathy in children. B. Woźniewicz. Department of Paediatric Pathology, Medical School of Warsaw, Poland.

Precocious thymic atrophy was found in about half of 3000 consecutive necropsies. Advanced thymic atrophy (producing so-called thymic remnants or rudiments) was seen in 6% of cases including 3 of thymus dysplasia and 3 of athymia. In each case the peripheral lymphatic system was examined microscopically and, in some, by EM and cytochemistry. Severe thymic atrophy was associated with lymphadenopathy. It consists of T-zone atrophy, lymphocyte depletion, the appearance of lymphoblasts, immunoblasts, histiocytes, and Strernberg-like cells, incrustation of reticular fibres with PAS-positive deposits, and accentuation of the vascular pattern. It is suggested that thymic atrophy and immunological lymphadenopathy may precede malignancy. It was also shown that malignant lymphomas, leukaemias, and malignant histiocytic proliferations in children were associated with thymic atrophy in about 70% of cases.

Pulmonary sequelae of epidemic type-21 adenovirus infection: a 13-year follow-up. D. M. O. Becroft. The Princess Mary Hospital for Children, Auckland, New Zealand.

43 infants aged 3–18 months were admitted to hospital in 1965 with acute lower respiratory tract infections which ran a prolonged course. Type-21 adenoviris was isolated from 21 children and the outcome in 18 of these was reassessed in 1978.Three had died of respiratory disease. 15 were examined clinically and radiologically, and 11 had lung function tests. 11 had abnormal chest *x*-rays and, of these, 9 had bronchiectasis. Two of the 4 with normal chest *x*-rays had abnormal lung function tests. Bronchiolar obliteration was the most consistent pathological finding in the lungs of 5 cases and is the expected sequel of the bronchiolar mucosal necrosis of acute adenoviral infection. Bronchiectasis was found 4 months after the acute infection in one infant. Three persistently collapsed lungs, removed 1, 3, and 5 years after the acute infections, showed the secondary inflammatory changes in bronchi typical

of the follicular type of bronchiesctasis. Another lobectomy specimen obtained 12 years after the acute infection in an asymptomatic child had thin-walled dilated bronchi with little inflammation, i.e. a cystic or saccular bronchiectasis. The extent of early bronchiolar obliteration apparently determines the severity of chronic postadenoviral pneumopathy and the development of bronchiectasis.

Histology and ultrastructure of the prepubertal and pubertal testis following combination chemotherapy. M. Lendon and H. B. Marsden. Department of Pathology, University of Manchester, and Royal Manchester Children's Hospital.

The assessment of gonadal function has become increasingly important in children with acute lymphoblastic leukaemia as longer survival is achieved by the use of cytotoxic treatment. The deleterious effects of drugs—such as cyclophosphamide and chlorambucil—on men are well known. Reports on the testicular histology after this treatment in children are few and contradictory. Since mid-1977 we have studied bilateral testicular biopsies from 44 boys (27 prepubertal and 17 pubertal) with acute lymphoblastic leukaemia. All the boys had received a variety of therapeutic regimens. Each biopsy was assessed by light microscopical examination for the following histological parameters: leukaemic infiltration, interstitial fibrosis, basement membrane thickening, the presence or absence of Leydig cells, and the presence or absence of spermatogenesis. Two morphometric studies were performed—the mean tubular diameter and the tubular fertility index, and each biopsy was examined by electron microscopy.

Identification of Niemann-Pick disease. A. D. Bain and G. T. N. Besley. Department of Pathology, Royal Hospital for Sick Children, Edinburgh.

Review of congenital heart disease in Poland studied pathologically. K. Karczeński. Department of Pathomorphology, Institute of Paediatrics of the Medical School, Warsaw, Poland.

Congenital heart disease in Poland now occupies 4th place among the principal causes of death under 12 months of age and accounts for approximately 40% of all fatal congenital malformations. The number of cases of congenital heart disease in Poland for the last few years is still rising—in absolute and relative terms. The Institute of Paediatrics in Warsaw is the main centre in Poland for children with congenital heart disease. Congenital cardiovascular malformations have been encountered in 1276 cases out of 3792 consecutive necropsies performed on children. All the data presented are complete and unselected. The most common were: transposition complex—286 cases; septal defects—248 cases; Fallot's syndrome—220 cases. The different congenital cardiac complexes have been analysed and correlated with the sex and age distributions. The incidence of extracardiac birth defects accompanying cardiac defects was also analysed.

Gonadal infiltration in childhood leukaemia and lymphoma—a post-mortem survey. H. Reid and H. B. Marsden. Department of Pathology, University of Manchester, and Royal Manchester Children's Hospital, Manchester.

In children with leukaemia, extramedullary sites, in particular the CNS and more recently the testis, have been incriminated as causes of relapse. In view of the current interest in testicular disease in acute lymphoblastic leukaemia, a survey was undertaken to determine the exact incidence of gonadal infiltration from the necropsy files of the Royal Manchester Children's Hospital. There were 96 cases of leukaemia and lymphoma—65 boys and 31 girls. Sections of testes were examined for the presence and degree of infiltration, interstitial fibrosis, and assessment of numbers of spermatogonia. Sections of ovaries were examined for the presence and degree of infiltration by leukaemia and lymphoma.

Congenital cardiac malformation and ischaemic cerebral lesions. F. Ochsner, J. N. Cox, and B. Friedli. Institut Universitaire de Pathologie, Geneva, Switzerland.

An anatomical and statistical analysis of ischaemic cerebral lesions in association with various types of cardiac abnormalities are reported. There were 227 cases with ages ranging from birth to 20 years. The cerebral lesions encountered were grouped into five categories: (1) infarction (with or without thrombolism); (2) diffuse lamina; (3) focal lesions on the watershed areas; (4) venous thrombosis; and (5) lesions affecting the white matter and central nuclei. 27% of cerebral lesions were observed in this series. An attempt was made to correlate the various types of cerebral lesions with the types of cardiac malformations, taking into account those which were catheterised and/or operated upon. 20% of the cases presented cerebral anomalies and in 4% there were infectious complications; these were not included in the study.

A morphological classification of enterocolitis in infancy. K. Madi, C. M. Ávila, E. T. D. Ávila, D. de Paola. Departamento de Patologia, Universidade Federal do Rio de Janeiro, Brazil.

In a review of 1400 necropsies, 380 cases of intestinal inflammatory lesions were selected and classified on a morphological basis. Most cases were in infants between 2 and 6 months of age. Malnutrition was common. The lesions were classified as follows: (1) *Enterocolitis* (*EC*) *with predominance of acute changes*: (a) catarrhal EC; (b) typhoid-like EC; (c) necro-haemorrhagic EC (diffuse or patchy necrosis, small bowel predominance); (d) papulo-necrotic EC (focal, nodular, or follicular necrosis, large bowel predominance); (e) ulcerated EC. (2) *Enterocolitis* (*EC*) *with predominance of chronic changes*: (a) chronic atrophic EC (sprue-like atrophy in the small bowel; mucosecretory atrophy in the large bowel; (b) granular-cystic colitis (finely or grossly granular and ulcero-granular); (c) chronic ulcerative colitis; (d) chronic follicular EC. It is believed that a single type of lesion may be produced by different agents, and conversely that single agent may produce various types of lesions, which may occasionally be present at the same time in an individual patient.

Renal polycystosis induced by prednisolone tertiary butyl acetate in the newborn rat. R. W. Whitehouse, R. G. Lendon, and M. Lendon. Departments of Anatomy and Pathology, University of Manchester.

64 litters of newborn Sprague-Dawley rats were culled to 10 per litter shortly after birth. Seven from each litter were injected IM on the first day of extra-uterine life with either 66 mg/kg or 150 mg/kg prednisolone TBA (Codelcortone—TBA), and the remaining 3 with an equivalent volume of isotonic saline. Animals were killed on days 4, 8, 10, 12, 14, 16, and 20. The development of the induced renal cysts was studied histologically and histochemically. Cysts of the ampullae, collecting ducts, distal and proximal tubules, and glomeruli were found and their temporal sequence was determined. Quantitative estimation of glomerular numbers using an acid digestion technique showed a reduction of glomerular numbers in corticosteroid-injected animals, with apparently little new glomerulus development after day 8.

Influence of endogenous and exogenous factors on the morphology of lymphoid organs. J. Huber, E. Gelfand, and B. Wilson. Department of Pathology and Immunology, The Hospital for Sick Children, Toronto, Canada.

Lymphoid organs belong to a dynamic system and vary tremendously, both morphologically and functionally under different circumstances. As a consequence, the microscopical appearance may be deceptive and confusing. Major considerations in interpretation are: (1) the quantum expansion of the lymphoid system in the first few months of life; (2) the changes in the microenvironment such as local infections that affect regional nodes; (3) the generalised changes in response to systemic infection, chronic illness, and drug administration—for example corticosteroids, and (4) the limited capacity for routine histological stains in assessing functional status. Examples of developmental and acquired changes will be illustrated by comparing neonatal with postneonatal lymph nodes, also of lymph nodes from infected and noninfected sites, and lymph nodes before and after corticosteroid treatment. Finally, comparison will be made of thymus from biopsy and necropsy. These examples emphasise the caution with which static histological appearances must be interpreted, and the necessity to evaluate complete clinical information before drawing final conclusions.

Multiseptate gallbladder in cystic fibrosis. M. F. Kamal. Department of Pathology, University of Manchester.

Granular-cystic colitis. Pathological changes seen in infants with persistent or chronic diarrhoea in Rio de Janeiro. K. Madi, C. M. Ávila, E. T. D. Ávila, and D. de Paola. Departamento de Patologia, Universidade Federal do Rio de Janeiro, Brazil.

18 cases were selected from 380 necropsies on children with persistent (>15 days) or remittent diarrhoea. The mucosa presented a granular aspect with cysts. The lesions were graded *finely granular*, *grossly granular*, or *ulcero-granular*. In the first two forms, ulcerations could be detected only under the dissecting microscope or histologically. The appearances can be distinguished from the so-called colitis cystica superficialis seen in pellagra. The pathological picture is quite different from chronic ulcerative colitis of older children or adults, and from nodular lymphoid hyperplasia. Pathogenic micro-organisms were detected in only a few cases. Not uncommonly acute (necrotic) and chronic lesions are associated. All children examined had severe (protein-calorie) malnutrition but not necessarily pellagra. The authors believe this to be a non-specific reaction of the large bowel to prolonged action by one or several noxious agents, having malnutrition as a background.

Mucucutaneous candidiasis complicating neonatal intensive care. P. J. Kelehan and A. J. Barson. Department of Pathology, St Mary's Hospital, Manchester.

Three infants are described who died with widespread *Candida albicans* infection of the skin, and intestinal and respiratory tracts. They were 27–30 weeks in gestational age and survived from 10 to 27 days. All were treated in an intensive care unit for respiratory difficulty and jaundice, and all required mechanical ventilation and exchange transfusions. One infant died of necrotising enterocolitis, another of intraventricular haemorrhage, and the 3rd primarily of the candidiasis. A desquamative, erythematous rash covered the skin over most of the thorax and abdomen. It is thought that the infection began initially beneath elastoplast required for securing umbilical catheters, spreading elsewhere either via the umbilical vessels or the endotracheal tube. All were treated for bacterial sepsis and all showed extreme thymic involution. Such generalised mucocutaneous candidiasis appears to be a particular complication of prolonged intensive care of the ill premature infant.

Examination of the abortuses resulting from prenatal diagnostic surveillance for neural tube malformations. K. M. Laurence and J. O. Dew. Welsh National School of Medicine, Cardiff.

Antenatal diagnosis of the congenital nephrotic syndrome. A. H. Cameron, M. Crawley, H. O. Nicholson, D. I. Rushton, and R. H. R. White. Birmingham Children's and Maternity Hospitals, Birmingham.

The mononuclear phagocyte system—a hitherto unrecognised precursor cell. I. I. Smith, A. E. Dewar, and A. E. Stuart. Departments of Pathology, Royal Hospital for Sick Children, Edinburgh, and Universities of Edinburgh and Newcastle.

It is now established that the concept of a *reticulo-endothelial system* is erroneous. Numerous experiments on animals in different centres, including our own, have shown that phagocytosis of large particles is a property of tissue macrophages and circulating monocytes, which is not shared by endothelium or the fictitious 'reticulum cell'. Our studies in man of idiopathic thrombocytopenic purpura and autoimmune haemolytic anaemia confirm this. The modern concept of a *mononuclear phagocyte system* envisages tissue macrophages as being derived from circulating monocytes, and ultimately from bone marrow precursor cells. It does not preclude the possibility of local replication of macrophages, but relegates this to a minor role, at least under normal and most experimental conditions. Nevertheless, the failure to observe orthodox blood monocytes transforming into Kupffer cells has led to controversy regarding this generalisation. Our studies in mice treated with the simple lipid cholesterol oleate first showed a cell type, apparently transforming into Kupffer cells, that lacked the morphological or cytochemical characteristics of orthodox monocytes. Subsequently, this was also observed in untreated mice. Ultrastructurally, this cell resembles a lymphocyte before it undergoes this transformation. It can be suggested that this lymphocytoid cell is the true promonocyte and that this hitherto unrecognised cell plays a more general role in repopulating tissues with macrophages.

Functional control of fetal lung growth. J. S. Wigglesworth and R. Desai. Institute of Child Health, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS.

Improved lung expansion in premature newborn rabbits after tracheal instillation of synthetic surfactants. G. Grossmann and I. Larsson. Department of Paediatric Pathology, Karolinska Institutet, and the Swedish Institute for Surface Chemistry, Stockholm, Sweden.

Earlier experiments have shown that neonatal lung expansion can be facilitated by tracheal instillation of 'natural surfactant', containing phospholipids (8 mg/ml) and protein (0·6 mg/ml). In order to analyse whether the surface properties of natural surfactant can be imitated by a protein-free synthetic lipid preparation, lipids normally present in the fetal pulmonary fluid at term were analysed in various combinations with the pulsating bubble technique. An emulsion comprising 8 mg dipalmitoyl phosphatidyl choline, 2 mg phosphatidyl glycerol, 0·1 mg palmitoyl lysophosphatidyl choline, and 5 mg palmitoleic acid in 0·02 ml soy bean oil and 1 ml saline was found to have *in vitro* surface properties similar to those of natural surfactant. In subsequent experiments, 50 μl of the natural or the synthetic surfactant preparation were instilled in the trachea of premature rabbit neonates, delivered on day 27 of gestation (term = 31 ± 1 days). Pressure/volume recordings showed significantly increased pulmonary distensibility and improved stability on deflation in both treated groups, compared with untreated controls. The recordings from neonates treated with the synthetic preparation were similar to those obtained from litter-mates receiving natural surfactant. These findings suggest that tracheal instillation of such a protein-free synthetic lipid emulsion at birth might be used as a prophylaxis against respiratory distress in premature infants.

Effects of pulsed steroids and plasmaphoresis on a case of proliferative glomerulonephritis with crescents evaluated by renal biopsies. C. R. Tribe and G. B. Haycock. Southmead Hospital, Bristol.

Size of renal glomeruli in children with congenital heart disease and in unexpected deaths in infancy. S. Variend. Children's Hospital, Sheffield.

Large renal glomeruli have previously been associated with congenital cyanotic heart disease. The precise mechanism for the glomerulomegaly is still not clear, but one theory suggested is chronic hypoxia. The measurement of the size of glomeruli in a large number of cases of cyanotic congenital heart disease, 'cot death', and cases not apparently associated with chronic hypoxia was prompted by the suggestion that chronic hypoxia may be an important underlying mechanism in 'cot death'. 400 cases ranging in age from one week to one year were studied. In each case the areas of 10 glomeruli were measured from the mid-cortex in standardised normal sections. Tracings were made of the projected images of the glomeruli at constant magnification and the areas measured with a planimeter. This study confirms the presence of large glomeruli in many cases of cyanotic congenital heart disease, and concludes that a small but significant proportion of cases of 'cot death' also have large glomeruli. Some cases of endocardial fibroelastosis also showed a similar lesion. It is suggested that, while chronic hypoxia may be responsible for the glomerular enlargement, the elucidation of the precise mechanism responsible might help more in our understanding of 'cot death'.

Prune belly syndrome. R. N. Laurini and E. Gray. Royal Hospital for Sick Children, Glasgow, and University of Abderdeen.

Prune belly syndrome (PBS) is a rare entity classically described as a triad of absence or hypoplasia of abdominal muscles, urinary tract abnormalities, and cryptorchidism. The condition is almost entirely limited to males and can be associated with anomalies of other organs. Chromosomal anomalies are exceptional and only twice PBS has been reported affecting a family. We report the findings in 11 cases of PBS in males, including family history, chromosomal studies, and placental findings in some of the cases.

Congenital ciliary anomalies and respiratory disease. J. M. Sturgess, J. Chao, and J. A. P. Turner. The Hospital for Sick Children, Toronto, Canada.

The mucociliary clearance mechanism in the lung is dependent on the propulsive force of cilia to promote the flow of mucus in the respiratory tract. Recent evidence has implicated specific defects in cilia as the basis of human respiratory disease, such as that seen in Kartagener's syndrome. Two types of defect were identified at the ultrastructural level in the human ciliary axoneme. The lack of dynein arms on the outer microtubular doublets of the ciliary axoneme is described and results in immotile cilia. Recently, we found a second abnormality in human cilia, a defect in radial spokes which is identified by the altered radial symmetry of the ciliary axoneme and the eccentric central tubules and sheath. Both defects are considered to be congenital anomalies of cilia. These defects cause ciliary dysfunction and result in similar clinical consequences of chronic upper and lower respiratory disease from early childhood either alone or as the triad of chronic sinusitis, bronchiectasis and situs inversus, characteristic of Kartagener's syndrome.

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Abnormalities of the complement system in children with liver disease. V. F. Larcher, J. Wyke, A. P. Mowat, and R. Williams. Department of Child Health and Liver Unit, King's College Hospital, London SE5.

Abnormalities of the complement system have been described in adult liver disease (Charlesworth *et al.*, 1977). We studied both classical and alternate pathways of complement in 84 children with liver disease and in 30 control children. Classical pathway components were measured by haemolytic or immunodiffusion techniques. Alternate pathway activity was measured by determination of yeast opsonisation index (0·1 = mean number of yeasts phagocytosed per normal polymorph in presence of test serum; Soothill and Harvey, 1977). High values of yeast opsonisation ($P<0·001$) were found in 10 preoperative cases of biliary atresia (0·1 = 5·38 ± 0·70 mean ± 2 SD) compared with controls (4·3 ± 1·16 mean ± 2 SD). Defective opsonisation (0·1 = 1·66 ± 1·16 mean ± 2 SD; $P<0·001$) and low levels ($P<0·001$) of complement factors, 3, 4, 5, B, and D were found in 10 children with fulminant hepatic failure. Normal values were found in 2 survivors and in 4 children with previous hepatic failure. Eight further patients (2 after successful surgery for biliary atresia; 2 untreated chronic active hepatitis; 4 corticosteroid-treated chronic active hepatitis) had defective opsonisation with or without changes in other complement components.

Serum complement abnormalities are common in children with liver disease, but more study is necessary to elucidate their role in pathogenesis of liver disease or its complications.

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Hepatic collagen synthesis and its modification by colchicine in a rat model of cirrhosis of the liver. M. S. Tanner, D. Jackson, and A. P. Mowat. Department of Child Health, King's College Hospital Medical School, Denmark Hill, London SE5.

An animal model of hepatic cirrhosis, in which rats pretreated with oral phenobarbitone inhale carbon tetrachloride twice weekly, was used to study hepatic collagen synthesis and its modification by colchicine. Hepatic collagen, measured as protein-hydroxyproline, doubled after 4 weeks' exposure, and free proline increased concomitantly. The activity of peptidyl prolyl hydroxylase (PPH), an enzyme catalysing an early step in collagen synthesis, increased approximately 5-fold, and this higher activity preceded the increase in collagen, PPH activity showed considerable lability, an increase in activity occurring between 24 and 48 hours after each exposure to carbon tetrachloride. Colchicine, 100 μg given daily by orogastric tube, for 6 days a week, partially prevented this collagen deposition. The liver collagen content, in μmol hydroxyproline /g wet liver, for control rats was 1·007 ± 0·109; for rats given 4 weeks' carbon tetrachloride it was 2·086 ± 0·416; for rats given 4 weeks' carbon tetrachloride and colchicine it was 1·309 ± 0·077. PPH activity was similar in the last two groups. Colchicine treatment did not affect growth.

Colchicine, which decreases net collagen deposition both by microtubular inhibition and by stimulating collagenase, may impede the progression of chronic liver disease to cirrhosis.

The Poland anomaly and allied disorders. T. J. David. Bristol Children's Hospital.

Clinical evaluation and comparison of the Infrasonde, Arteriosonde, and mercury sphygmomanometer in measurement of blood pressure in children. J. M. Savage, M. J. Dillon, and J. F. N. Taylor. Renal and Thoracic Units, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH. To be published in full in the *Archives*, 1979, **54**, 184–189.

Renin and angiotensin in normal, prepubertal girls. O. R. C. Smales, F. Broughton Pipkin, and M. O'Callaghan. Departments of Child Health and Obstetrics and Gynaecology, City Hospital, Nottingham.

Renin and angiotensin II (AII) levels were measured in 30 normal girls, 2 to 11 years old. The older girls had lower plasma renin concentrations (PRC) which were not significantly different from adult levels. Plasma AII levels however were significantly higher in all children ($P<0\cdot001$). PRC and AII levels were lower when diastolic blood pressure was greater than 70 mmHg than when it was less than 70 mmHg. This difference was only statistically significant for PRC.

Regression analysis showed that plasma renin activity was inversely related to serum sodium levels and directly proportional to the ratio serum sodium:potassium ($P<0\cdot025$ for both). PRC was also proportional to serum potassium ($P<0\cdot02$). Plasma AII was inversely proportional to serum sodium ($P<0\cdot025$) and related to PRC ($P<0\cdot05$).

Simultaneously measured renin and AII levels have not, to our knowledge, been previously reported for this age group. The results show that the high levels seen in infancy remain above adult levels during the first few years of life. However, it appears that the stimuli of relative hypotension and hyponatraemia are controlling factors at these ages as well as in adulthood.

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Which 'small-for-dates' infants are malnourished? O. G. Brooke and Fiona Butters (introduced by R. J. West). Department of Child Health, St George's Hospital, London SW17.

In an attempt to improve diagnostic precision in assessing small-for-dates babies, we measured upper arm muscle and fat area (derived from mid-upper arm circumference and skinfold measurements) in 221 unselected term neonates. Results were expressed per unit upper arm length. Irrespective of birthweight, infants were defined as 'malnourished' if arm muscle *and* arm fat areas fell more than 1 SD below the mean, or if either area alone fell more than 2 SDs below the mean. By these criteria, 22 infants were malnourished (birthweight range 2100–3570 g). A further 21 infants were small-for-dates by current definition, being <10th centile of weight for gestational age, but not malnourished. We called these 'normal small infants'. There was a predominance of Asians in each group. 14 out of the 22 'malnourished' infants had obstetric complications which could impair fetal growth (hypertension, APH, toxaemia, anaemia). Only one of the 'normal small infants' had any such complications. These differences were highly significant ($P<0\cdot001$). Skinfold measurements alone gave poor discrimination between 'malnourished' infants with a bad obstetric history and 'normal small infants' without obstetric complications. Birthweight only identifies the grossest forms of intrauterine malnutrition and should no longer be the sole criterion for defining the small-for-dates baby.

Circadian rhythms of melatonin and cyclic-AMP in neonates. A. Evans,* N. D. Carter,* O. G. Brooke,* and J. Smith.† Department of Child Health, St George's Hospital Medical School, London SW17 0RE* and the School of Pharmacy, University of Bradford.†

Circadian variations in blood and urine levels of cyclic-AMP (Holmes and Hamadah, 1977) and melatonin (Wurtman and Moskowitz, 1977) is well documented, and the melatonin rhythm is maintained in pregnant women (Matthews *et al.*, 1978). We investigated these rhythms in neonates and attempted to assess the influence of maternal circadian activity of melatonin on rhythm development in the baby. Blood was taken for serum melatonin estimation from the umbilical cords of 26 normal term infants, and paired samples of cord and maternal blood samples were taken from a further 20 normal infants. Melatonin was measured by radioimmunoassay. Cord blood from another 71 term normal infants was assayed for cyclic-AMP by a competitive protein binding assay.

The results of 26 cord blood melatonin assays (Table 1) show a clear circadian rhythm. The daytime (0800–2000 hours) levels are significantly lower than the night-time (2000–0800 hours) ones ($P<0\cdot05$). Assay of the paired samples showed no significant correlation between cord and maternal serum melatonin levels. The maternal levels showed no carcadian rhythm.

Cord serum cyclic-AMP levels showed a circadian rhythm (Table 2). The morning (0000–1200 hours) levels are significantly greater ($P<0\cdot001$) than the evening (1200–2400 hours) ones.

Table 1 *Melatonin levels of 26 term infants*

Hours	2400–0400	0400–0800	0800–1200	1200–1600	1600–2000	2000–2400
n	3	2	4	8	3	6
Melatonin pg ml^{-1} (mean ±1 SD)	61·7± 55	3·5± 4·9	4·0± 8·0	15·0± 24·2	1·3± 2·3	37·3± 29·5

Table 2 *Cyclic-AMP levels of 54 term normal infants*

Hours	2400–0400	0400–0800	0800–1200	1200–1600	1600–2000	2000–2400
n	13	13	6	20	11	8
C-AMP pmol ml^{-1} (mean ± 1 SD)	14·3± 18·7	84·6± 92·5	12·0± 14·1	25·3± 34·1	27·2± 43·3	0·6± 1·2

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Stools in infancy. Frequency and weight, water, and energy content. N. Lemoh and O. G. Brooke. Department of Child Health, St George's Hospital, London SW17.

There is little information on the frequency of defecation in normal infants and toddlers and on their stool weight, water, and energy content. This study was undertaken to provide such data without any attempt being made at energy balance study.

Stools were collected in rayon napkin liners during a period of 3–9 days from 53 healthy infants and toddlers aged 3 days to 2 years, who were either in their own homes or in hospital as social admissions. Those in hospital were given a reasonable period for adjustment before being studied. In a preliminary study a method of stool collection was established. The aim of this was to observe the effect on weight of wet stools exposed to wet napkins. Preweighed samples of wet stools in liners were incubated at room temperature for 2 hours in previously weighed disposable napkins adequately soaked with 0·9% saline solution. The result showed no significant change in stool weight or napkins. Subsequently, freshly passed stools were frozen at −24°C, weighed wet, freeze-dried for estimation of water content and for determination of total daily energy content. Neonates were all bottle fed and older infants were on a mixed diet. Infants with gastrointestinal disorders or other illness were excluded.

Results are given in the Table. There was a progressive decrease in stool frequency with age but there were wide variations between individuals. There was also marked variation in daily stool weight but little fluctuation in stool water content. The stool energy concentration tended to fall with increasing age.

Table *Stools in normal infants (mean, observed ranges, and SD of various measurements)*

	Age		
	3 days–4 weeks	*1–12 months*	*12–24 months*
No. of infants	25 (22*)	11 (8*)	17 (12*)
Interval between stools (hours)	6·8 (3–20)	11 (7–36)	15 (7–43)
Daily mean wet weight (g)	26 (4·6–58)	31 (19–70)	71 (14–133)
% water	73±4·2*	75±3*	74±4*
Daily mean energy per gram (kcal)	7·7* (5·2–12·6)	6·6* (4–11·7)	6·0* (2–10)
Total daily mean energy (kcal)	46·7* (22–93·7)	43·7* (11–73)	62* (10–130)

*Number of infants studied and the corresponding results.

Response of term babies to a warm environment. N. Rutter and D. Hull. Department of Child Health, Nottingham University. To be published in full in the *Archives*, 1979, **54**, 178–183.

Neonatal form of dystrophia myotonica. A report of 5 cases in preterm babies and a review of the literature. R. G. Pearse and C. J. Höweler. Department of Paediatrics and Neurology, Sophia Children's Hospital, and Academic Hospital, Erasmus University, Rotterdam, The Netherlands. To be published in full in the *Archives*, 1979, **54**.

Adhesion of Escherichia coli (EC) to buccal epithelial cells (BEC). D. C. A. Candy, J. Chadwick, W. C. Marshall, and J. T. Harries. The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH, and Institute of Child Health, Guilford Street, London WC1.

The pathophysiological mechanisms operating in diarrhoeal states are currently under intense study, and this is particularly the case for the mechanisms involved in the adhesion of bacteria to epithelial cells: adhesion to epithelial cells is a prerequisite to intraluminal colonisation and the subsequent sequence of events which induce small intestinal secretion and diarrhoea. We studied adhesion of EC to human BEC using a modification of the method of Ofek *et al.* (1977).

We established that a strain of EC (026:K60) known to adhere to fetal intestine (McNeish *et al.*, 1975) also adhered to BEC, and that another non-adhesive strain failed to do so. Colonies of EC were isolated from the stools of 13 healthy infants, and 2–6 colonies in 10 of these infants were the nonadhesive organisms (4 of these strains were designated as 'enteropathogenic' on the basis of their agglutinating properties). Agglutinable EC isolated from the stools of 9 children with diarrhoea were studied and 8 were adherent to BEC. Adhesion was partially or completely inhibited by D-mannose, and EC isolated from 2 patients with diarrhoea adhered to their own BEC but not to donor cells.

These results suggest (1) 'enteropathogenecity' of EC is not synonymous with their agglutination properties, (2) EC binds to specific mannose-like receptor sites, and (3) the BEC system may be a simple test to assess whether a bacteria is 'enteropathogenic'.

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Enteropathogens in preschool children and their pets. R. W. Newton, R. J. Pugh, and I. D. Leighton (introduced by T. Turner). Department of Paediatrics and Bacteriology, Hull Royal Infirmary, Anlaby Road, Hull.

During a 4-month period, 152 consecutive preschool children attending a general outpatient clinic were screened for intestinal parasites and enteropathogenic bacteria. Each child was requested to submit 3 fresh stool specimens and also 3 stool specimens from any animal with which the child had significant contact. Careful record was made of age, social class, type of accommodation, and history of pica in the child. Inquiry was made into the health of any pet.

Of 78 children with no family pets, 34 (44%) failed to submit specimens, while 23% submitted 3 specimens. Only one child of the 44 submitting specimens had a significant culture. 74 children with pets entered the study; 51 (60%) failed to submit specimens while 12 (16%) produced 3 specimens. Among the 23 children submitting specimens 2 were found to have *Giardia lamblia*, one pathogenic *Escherichia coli*, and one *Salmonella typhimurium*. 12 dogs had stools submitted; 2 were infestated with *G. lamblia*, while a 3rd had *S. typhimurium*. Two children associated with these pets had recurrent diarrhoea, while a 3rd had the same pathogen (*S. typhimurium*). Other animals including cats, budgerigars, and rabbits failed to produce any positive pathogens.

This study shows the difficulty of patient and pet compliance and confirms that the presence of enteropathic bacteria and other parasites is more likely in children in regular contact with family pets, although both the children and pets may well be asymptomatic.

Nebulised salbutamol in the treatment of acute asthma in children. J. B. G. Watson and Olga M. Bannister. Departments of Paediatrics and Physiotherapy, Children's Hospital, Sheffield S10 2TH.

A PGS compressor unit with a Bird's nebuliser was used to administer nebulised salbutamol or placebo to a group of children with acute asthma in a double-blind trial. The salbutamol group showed a greater rise in peak expiratory flow rate (PEFR) (67 l/min) compared with the placebo group (21 l/min) $P<0 \cdot 005$. A further 57 patients had 190 doses of nebulised salbutamol and the mean rise in PEFR was 55 l/min. When IPPB was used to administer the nebulised solutions, the salbutamol group showed a mean rise in PEFR of 50 l/min compared with 10 l/min in the placebo group. Salbutamol administered by nebulisation offers an effective alternative to parenteral treatment for children with asthma. As a result of nebulised treatment fewer children required parenteral therapy in 1977 compared with 1975.

Bronchodilator effects of nebulised chlorpheniramine in childhood asthma. R. C. Groggins, A. D. Milner, and G. M. Stokes. Queen's Medical Centre, Nottingham.

Previous workers have failed to demonstrate a bronchodilator response to antihistamines in childhood asthma, in doses which did not produce side effects. However, a study on adult asthmatic subjects has shown that chlorpheniramine delivered intravenously is an effective bronchodilator (Popa, 1977). We investigated the effect of nebulised chlorpheniramine in a group of 10 asthmatic children aged between 8 and 14 years (mean 11). Response to treatment was measured with a Wright's peak flow meter and FVC and $FEV_{0 \cdot 75}$ were measured using a Morgan wet spirometer. Measurements were made before and for 2 hours after inhalation of the drug. At the end of 2 hours the children inhaled nebulised salbutamol (5 mg in 2 ml water) and lung function tests repeated after 15 min. Children attended on 3 occasions and received 2, 4, and 8 mg chlorpheniramine successively.

Bronchodilatation was observed, usually within 2 min of the inhalation of chlorpheniramine, and reached a plateau by 45 min. The response to 4 and 8 mg was similar with a greater than 30% improvement in $FEV_{0 \cdot 75}$ and PEFR response to 2 mg was less dramatic, with improvements of 15–20%. The only side effect was that of coughing, and each patient coughed at least once.

Antihistamines if delivered by appropriate routes and in appropriate doses do produce bronchodilatation in children with asthma.

Reference

Popa, V. T. (1977). Bronchodilating activity of an H_1 blocker—chlorphenramine. *Journal of Allergy and Clinical Immunology*, **59**, 54–63.

Hyposensitisation in house dust mite sensitive childhood asthma. J. O. Warner, J. F. Price, and E. N. Hey. Respiratory Unit, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

Hyposensitisation with *Dermatophagoides pteronyssinus* tyrosine absorbate in asthmatic children shown to be *D. pteronyssinus* sensitive by bronchial provocation tests (BPT), was shown to be effective in a double-blind controlled trial. Treated children (27) used less medication while maintaining clinical and lung function improvement compared with controls (24). These children responded to *D. pteronyssinus* injections alone despite the fact that most reacted to other inhalant antigens on prick skin tests. This confirms that *D. pteronyssinus* is the predominant antigen responsible for asthma in British children. In most children the benefit occurred despite no change in immediate response on BPT but the late reaction was lost in half the patients and these patients had the greatest symptomatic improvement. This confirms the importance of late reactions in childhood asthma.

Postprandial total serum bile acid concentrations in cystic fibrosis. Bryan J. Starkey and Mary C. Goodchild.Department of Clinical Chemistry, Queen Elizabeth Hospital, Birmingham B15 2TH.

The efficacy of a single 2-hour postprandial total serum bile acid (t.s.b.a.) concentration in the early detection of liver disease in cystic fibrosis (CF) was assessed. 27 CF patients (aged 4–27 years), 21 age-matched controls, and 40 healthy adults (aged 19–52 years) were studied. Venous blood samples were drawn in the morning, 2 hours after ingestion of a weight-related chocolate stimulus. T.s.b.a. concentrations were determined by the method of Mashige *et al.* (1976) and conventional serum liver function indices by standard methods. T.s.b.a. concentrations expressed as mean ± 1 SD (μmol/l) were: 27·0 ± 26·4 (CF patients), 19·9 ± 5·5 (age-matched controls), and 17·3 ± 4·5 (healthy adults). Most CF patients, therefore, had normal t.s.b.a. concentrations.

Six results in the CF group deserve comment: 2 patients with established liver disease did have abnormally high t.s.b.a. concentrations of 56·0 and 150·0 μmol/l; 3 patients with t.s.b.a. concentrations within the normal range were thought, by other criteria, to have liver disease; one patient, in whom the t.s.b.a. concentration was raised (42·0 μmol/l) had no other finding suggestive of liver involvement.

Thus, a single 2-hour postprandial t.s.b.a. concentration appears not to be particularly informative in CF. Wider investigations of bile acid metabolism, including sequential studies, may be necessary to elucidate the size and distribution of the bile acid pool, at varying ages, in this disease.

Reference

Mashige, F., Imai, K., and Osuga, T. (1976). A simple and sensitive assay of total serum bile acids. *Clinica chimica acta*, **70**, 79–86.

Release of endogenous secretin in children with cystic fibrosis. J. McKiernan, J. King, E. J. Hiller, and D. Johnston. Department of Child Health, Nottingham University, and The City Hospital, Nottingham.

The introduction of acid to the duodenum, in health, results in a brisk rise in plasma secretin levels. This endogenous secretin stimulates pancreatic secretion of water and bicarbonate, which neutralises the duodenal acid and inhibits further secretin release. As most children with CF have pancreatic exocrine insufficiency, we studied the pattern of secretin release in this condition. Nine children with CF were studied, all of whom were considered to have pancreatic exocrine insufficiency. Two different acidic drinks were given—0·2 M citric acid and 20% glucose, and pure lemon juice. Plasma secretin was measured before and after the drinks by radioimmunoassay. In only one case was there basal hypersecretinaemia (i.e. >60 pg/ml). The children who received the citric acid and glucose mixture showed a mean basal and mean peak plasma secretin of 37 and 120 pg/ml respectively. The values in the children who took citric acid alone were 34 and 48 pg/ml respectively. Thus both groups showed a positive response which was significantly greater in the citric acid and glucose group ($P<0·05$). These preliminary studies provide some new information of the regulation of pancreatic secretion in disease.

Bronchial allergy in children with cystic fibrosis. J. F. Price, P. H. Weller, S. A Harper, and D. J. Matthew. Respiratory Unit, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

Patients with cystic fibrosis have a high prevalence of positive skin prick tests to common inhaled antigens, but the importance of bronchial allergy in the disease is uncertain. We have investigated the response to antigen inhalation and exercise, and symptoms of respiratory allergy in a group of children with CF. 10 of 15 CF children with positive skin tests gave an immediate bronchial response to the antigen inhaled, 5 of them also gave a late (4–8 hour) response; however only one gave a history of asthma. In 6 patients tested with *Aspergillus fumigatus* the bronchial response varied, 2 were negative, one gave an immediate response, and 3 gave a dual (immediate and late) response. None of the children showed the characteristic pattern of response to exercise seen in asthmatic patients, an initial rise in peak flow rate (PFR) followed by a fall of greater than 14% below the resting level. Two patients showed an abnormal rise in PFR during exercise, a pattern previously described in CF.

The results suggest that bronchial allergy, immediate and late, does not completely explain susceptibility to asthma, and that other factors including perhaps the type of bronchial reactivity shown by bronchoconstriction after exercise may be required.

Growth patterns in children with malignant disease. N. K. Griffin and Jane Wadsworth. The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH, and St Bartholomew's Hospital, West Smithfield, London EC1A 7BE.

Short stature has been described as a complication of malignant disease in childhood. We studied 71 children with leukaemia and 24 with extracranial solid tumours and compared their growth with normal children for age and sex. Variables studied included diagnosis, radiotherapy field and dose, duration of chemotherapy, and the patient's age and sex. Children with leukaemia grew at a reduced rate in the year after presentation, and had a mean height after one year that was 0·41 SDs below their value at presentation ($P < 0 \cdot 001$). This effect was related to cranial and craniospinal irradiation, and was particularly pronounced after craniospinal irradiation. After one year from presentation growth rate was normal in all groups of patients, with no evidence of 'catch-up growth'. Failure of normal growth in the first year of treatment was observed in 59 of 65 patients who had received cranial or craniospinal irradiation.

It is concluded that prophylactic central system irradiation in leukaemic children causes a transient reduction in growth rate, but that the effect on eventual height attained is likely to be small.

Investigation using psychological tests in children with recurrent abdominal pain of nonorganic cause. R. H. Davies, St David's Hospital, Bangor, and E. Knassel, Department of Psychology, University College of North Wales, Bangor.

Twenty children with recurrent abdominal pain of nonorganic cause were compared with 20 children with appendicitis. They were subjected to Eysenk personality inventories, social maturity scales, the family relations test, the Rep test, and the self as implied pole test. Results showed the subjects were not different from the controls in the Eysenk extroversion/introversion or neuroticism tests. The subjects scored normally on the social maturity scales. In the family relations test they scored significantly lower than the controls in applying attributes and statements to themselves. In the Rep test they differed from controls in thinking themselves messy not tidy, failures not successes, but not unduly nervous. They scored significantly higher than the controls in the self as implied pole test. So the 'little bellyachers' were not neurotic, introverted, or socially immature, but although relatively confident they felt themselves untidy and failures; they dissociated attributes from themselves, and felt themselves poles apart from others.

Archives of Disease in Childhood, 1979, **54**, 166–167

Correspondence

Securing haemostasis during umbilical catheterisation in a neonate

Sir,
The most common method of maintaining haemostasis after catheterisation of umbilical vessels is to secure the catheter to the edges of the cord by using a nylon stitch. When the cord is initially cut to insert the catheter there may be some blood loss, and furthermore some blood may ooze at times in spite of a stitch. We recommend tying firmly a single knot at the base of the cord using wet ribbon gauze (15.2 × 1.0 cm). If this is done before the cord is cut, the catheters will pass without difficulty. Moreover should there be oozing from the cord the nursing staff have merely to tighten the knot before summoning medical help.

A. R. GATRAD AND A. H. GATRAD
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Henoch-Schönlein purpura after chickenpox

Sir,
Although Henoch-Schönlein purpura has been associated with many viruses, I have been unable to find a report of it after chickenpox.

An 8-year-old boy was admitted with a 36-hour history of abdominal pain, a tender right ankle joint, and a purpuric rash on his legs. 10 days earlier he had been unwell with a runny nose, sore throat, and cough, followed by a typical chickenpox rash, diagnosed by his family doctor.

On admission he complained of abdominal pain. He was apyrexial. There were a few submandibular nodes palpable and the tonsils were inflamed. Blood pressure was 110/70mmHg. There were scattered lesions over his back and anterior chest wall showing crust formation consistent with chickenpox. Over the buttocks and extensor surfaces of the legs he had a macular-purpuric rash and small haemorrhagic lesions. His right ankle joint was tender and slightly swollen. The platelet count was normal. There was a trace of proteinuria on the first day only.

The history, together with the physical findings, was typical of Henoch-Schönlein purpura.

He made an uneventful recovery during the next 4 days and has remained well since.

C. J. HALLE
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Incidence of dental caries in coeliac children

Sir,
As the result of comments made by parents at a Coeliac Society meeting to my paediatric colleague, Dr J. Kuzemko, concerning the rate of decay of their children's teeth, I have reviewed the developing dentitions of 12 of the coeliac children under his care at Peterborough during the last 5 years, for tooth quality and incidence of dental caries.

Coeliac disease was diagnosed at ages ranging from 6 months to 13½ years, and the children have been on a gluten-free diet for between 3 and 11 years. This is a small sample, but the caries experience of this group of children was certainly no worse than one would expect in a similar group of normal local children. Only one case of gross caries of the deciduous dentition was found, and the parent confessed to plying the child with sweets to compensate for the restricted diet. Thus a gluten-free diet does not appear to affect the quality of the developing teeth as far as caries resistance is concerned.

What does have an effect is if the condition is not diagnosed correctly soon after its onset in the early months or years, as the severe constitutional disturbance causes hypoplasia of those areas of the crowns of the permanent teeth which are calcifying at that time. During the first year this affects the anterior teeth and first molars, and these hypoplastic areas are prone to decay and spoil the appearance of the teeth.

We should be interested to learn of the experience of others in this perhaps neglected area.

E. D. FULSTOW
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Thorpe Road, Peterborough PE3 6DA

Atypical PKU with normal phenylalanine hydroxylase and dihydropteridine reductase activity *in vitro*

Sir,
In a recent report (*Archives*, 1978, **53**, 674) Schaub *et al.* described a patient with phenylketonuria who had normal hepatic activity of phenylalanine hydroxylase and dihydropteridine reductase. The patient responded to the administration of tetrahydrobiopterin (the natural cofactor of phenylalanine hydroxylase) by a rapid fall in plasma phenylalanine levels, and the authors postulate that their patient has a defect of biopterin synthesis.

Evidence for the existence of such a defect was obtained in two cases (those of Dr F. Rey in Paris and Dr K. Bartholomé in Heidelberg) who showed reduced serum and urine levels of total biopterin derivative (measured by *Crithidia fasciculata* assay) and an abnormal pattern of pterins on chromatography (Leeming *et al.*, 1976). The results of the *Crithidia* assays carried out by one of us (R.J.L.) in 1975 on the patient of J. Bartholomé (Kaufman *et al.*, 1975; Bartholomé *et al.*, 1977) have not been published and we should like to present them (Table).

Table *Levels of total biopterin derivative measured by Crithidia fasciculata assay in a patient with phenylketonuria (Bartholomé et al., 1977). Comparison with control values (mean ± SD)*

Subjects	*Serum* (µg/*l*)	*Urine* (*mg/l*)	*Liver (ng/g wet weight)*
Patient	0·2 0·7	0·09	16·7
Adult liver stored identically	—	—	550
Children with 'classical' PKU on diet	4·86±3·03	2·46±1·76	—
Normal children	1·78±0·79	—	—
Normal adults	1·81±0·64	2·1±1·32	—
Adults at abdominal operation	—	—	375±232

The levels of total biopterin activity in liver are markedly reduced, as are the levels in serum and urine. These results suggest that the patient, like that of Rey *et al.* (1977) and another reported recently by Kaufman *et al.* (1978), is deficient in biopterin. It remains to be explained why other measurements of hepatic cofactor activity failed to demonstrate an abnormality in Dr Bartholomé's case (Kaufman *et al.*, 1975; Bartholomé *et al.*, 1977).

Mr Leeming thanks Dr Bartholomé for allowing investigation of the patient.

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Dr Schaub and co-authors comment:

In our Short Report (*Archives*, 1978, **53**, 674), it was not our intention to claim the first description of a defect of biopterin synthesis. We only wanted to show that tetrahydrobiopterin (BH_4) can be absorbed from the gut and can be applied to lower the blood phenylalanine level in atypical PKU due to a suspected defect of biopterin synthesis.

Nevertheless, in the meantime we have been able to localise the metabolic block in our patient (Niederwieser *et al.*, 1979). Using high-voltage paper electrophoresis we found large amounts of neopterin in urine but no trace of biopterin or L-erythro-7, 8-dihydrobiopterin (BH_2). A comparable decrease of serum phenylalanine was observed after an oral administration of either BH_4, BH_2, or L-sepiapterin (Curtius *et al.*, 1979). The last is postulated to be an intermediate in the biosynthesis (Eto *et al.*, 1976; Gal *et al.*, 1978) of BH_2 from D-erythro-7,8-dihydroneopterin triphosphate (NH_2-P_3). Therefore, the metabolic block in this child must be between NH_2-P_3 and L-sepiapterin (Figure).

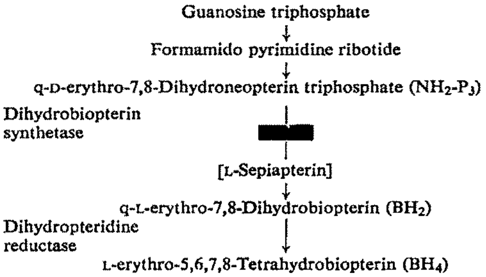
Guanosine triphosphate
Formamido pyrimidine ribotide
q-D-erythro-7,8-Dihydroneopterin triphosphate (NH₂-P₃)
Dihydrobiopterin synthetase
[L-Sepiapterin]
q-L-erythro-7,8-Dihydrobiopterin (BH₂)
Dihydropteridine reductase
L-erythro-5,6,7,8-Tetrahydrobiopterin (BH₄)

Figure *Biopterin biosynthesis from guanosine triphosphate and location of the dihydrobiopterin synthetase defect.*

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A. Niederwieser and H. Ch. Curtius
Department of Pediatrics,
University of Zurich, Switzerland

Archives of Disease in Childhood, 1979, **54**, 168

Book reviews

Primary Child Care. A Manual for Health Workers. By M. King, F. King, and S. Martodipoero. (Pp. 315; illustrated + tables. £2.00, soft cover.) Oxford University Press: London. 1978.

Maurice King's name became a byword in 1966 when he produced the 'Red Bible'—*Medical Care in Developing Countries.* Many would say that the production of this book was a turning point in the approach to health in developing countries. Since then Maurice King has written *Nutrition in Developing Countries* and a laboratory manual. Now, after a number of years of intensive work in Surabaya, he has brought out a book that may be more important in its direct effect than any of his previous writing. This new book is a system of primary care and is intended for adaptation and translation in whole or in part as one part of WHO's contribution to the International Children's Year—1979.

This book covers the diagnosis, understanding, and management of common conditions of childhood and, at the same time, shows how this can be built into a comprehensive system of child care with a necessary emphasis on prevention.

The author has taken great pains over detail in layout, choice of illustration, and simplicity of English. Although written for medical assistants it will be used by nurses, medical students, and doctors, many of whom in developing countries will for the first time possess their own book on child health, thanks to the low price of only £2.

This book is only part of a package or micro-plan and will be shortly followed by a teachers' guide which will contain 3000 multiple-choice questions and much other guidance material in the management of child health centres. Some 240 coloured transparencies of the common conditions so well managed in these books will also be available.

DAVID MORLEY

Surgical Conditions in Paediatrics. Postgraduate Paediatric Series. By H. Homewood Nixon. (Pp. 448; illustrated. £23.00, hardback.) Butterworth: London. 1978.

Is there any place today for the medical treatment of pyloric stenosis, or for local anaesthesia in its surgical treatment? What are the proved facts about the causation of intussusception, and what is the place of the barium enema in its diagnosis and management? What is the place, if any, for surgery in rectal prolapse, or in umbilical hernia? How to choose between the often very diverse treatments enthusiastically recommended for exomphalos? These are the sort of day-to-day questions about which the paediatrician so often longs to be able to button-hole a paediatric surgeon of experience and wisdom, and to pick his brains. Nixon's book, expressly written for medical paediatricians, goes a long way towards meeting this very need. His long experience at Great Ormond Street (his predecessor Denis Browne's aphorisms happily enliven and enlighten the text) is here distilled and in a most agreeable style. To cite one instance, if there is a more succinct and practical guide to the handling of the thorny subject of the undescended testicle, your reviewer has not met it. And as would be expected, the section on anorectal anomalie subject to which Nixon has contrib much, is beautifully lucid and pract Less so are only one or two sections, as the one on meconium ileus which to give a clear programme for hand these cases, or to explain when and the Gastrografin enema (described fir 1970 though here as 'recently') shoul used. Sternomastoid tumour, ano often debated condition, is not mentio perhaps being assumed to be nonsur anyway.

The illustrations are plentiful effective, the one on p. 371 sufficientl to have forced me to revise my hith simplistic teaching that there is no thing as tongue-tie.

DOUGLAS GAIRD

Shorter notice

Heart Disease in Infancy and Childh Third edition. Edited by J. D. K R. D. Rowe, and P. Vlad. (Pp. 1 illustrated + tables. £36.00, hardba Ballière Tindall: London. 1978.

A big welcome for the long awaited edition of this pioneering book! I bursting with new chapters and new id and for such a large book is remark up to date, containing many 1977 r ences. Some sections, and particularly approach to nomenclature, are ra confused, and many angiocardiogram poor. But the book remains a stan reference work, and a must for any lib of paediatrics or cardiology. Size apa could well be termed the paedi cardiologist's vade-mecum.

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1. Practical Therapeutics (1975) 10, 112.
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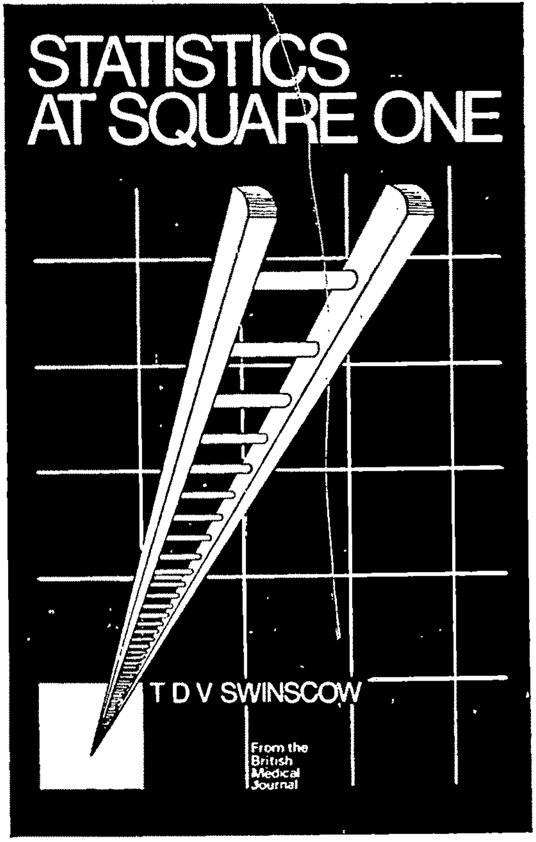

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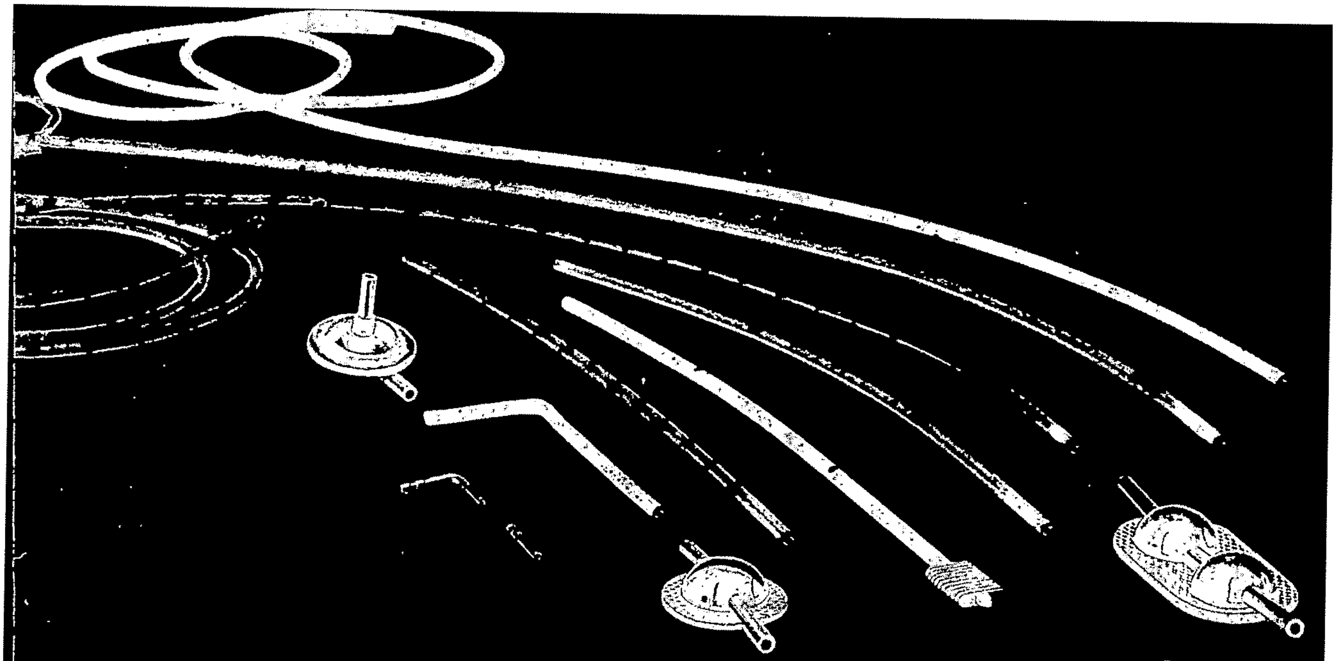

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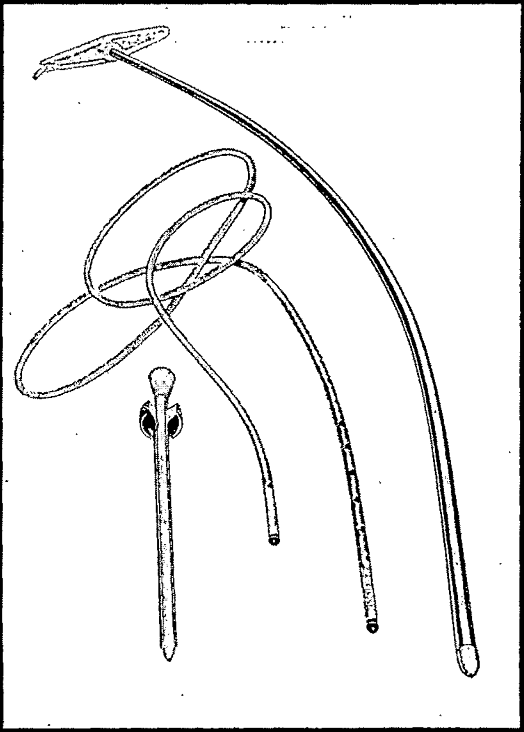

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Annotation

Genetic registers

Two-thirds of couples referred for genetic advice after the birth of an affected child were deterred from having further children when given high recurrence risks (greater than 1 in 10, and usually 1 in 2 or 1 in 4).[1] Thus in a sense, genetic counselling can prevent genetic disease by birth control; but there are also more opportunities for prenatal diagnosis and selective abortion, which can lead to compensatory birth of unaffected children. About 85% of relatives deemed to be at high risk of having a child with a serious genetic disorder have never been given counselling and are unaware of the risks,[2] and therefore genetic registers designed to improve ascertainment and follow-up of these individuals so that they may be offered genetic counselling, seem a reasonable idea.

In 1977 the Committee of the Clinical Genetics Society formed a Working Party in order specifically to consider: the nature of genetic registers, their value and potential application particularly with regard to the prevention of genetic disease; the place of registers for specific genetic disorders—such as Huntington's chorea—and genetic disorders in general where relatives may be at high risk; and the feasibility and acceptability of genetic register systems organised either nationally or locally. The chairman, Professor A. E. H. Emery, has just produced his report.[3]

Existing registers

At present 38 centres in Britain maintain registers primarily concerned with genetic disease so, in practice, the Working Party considered the direction in which we should go rather than whether or not we have genetic registers at all. Existing registers were designed with different functions in mind, and range from not much more than a simple refinement of normal medical records to what the Working Party calls preventive registers designed to improve the ascertainment and follow-up of individuals at risk of transmitting a serious genetic disorder to their offspring, so that they may be offered genetic counselling, including prenatal diagnosis if possible.

It is preventive registers and, to some extent, the large reference research registers that will have far reaching implications for the public and the medical profession. The report outlines three existing computer-aided registers as examples. The RAPID (Register for the Ascertainment and Prevention of Inherited Disease) system was first established in Edinburgh in 1970 and much of what is recommended by the Working Party seems based on this system. The Indiana MEGADAT (Medical Genetics Acquisition and Data Transmission) system collects and processes information on families with genetic disorders at the rate of 1500 per year, and by 1975 had already incorporated data on one-third of a million individuals. The Belgian National Register contains data on all persons (about 6000 a year) referred to any of the seven Belgian medical genetic centres. The last two are very large, multipurpose registers not planned or recommended for this country, and so debate will centre on the recommendations for preventive registers.

Approaching relatives

A particular problem with the establishment and use of genetic registers (dealing largely with dominant and X-linked recessive diseases) is that diagnosis of the disorder immediately generates important information on relatives who themselves have not sought medical advice. This creates the problem of how to approach family members. The index case has the right to refuse disclosure of his diagnosis to his relatives. Indeed a proportion will express this desire, but in his initial request the doctor may have already intimated that withholding permission to approach relatives could mean unnecessary suffering in the family. The patient now has this extra burden of responsibility to add to his problems. In their discussion of this and similar issues, the Working Party rightly concentrates on the role of the family doctor, so that relatives at high risk are contacted only with the express permission of both the index case and the relative's family doctor, through whom it is best to establish contact. Paediatricians and other specialists will also undoubtedly become involved, and if the activities related to the register are seen to be clearly within the general bounds of family health care, then the majority of families are likely to welcome both the approach and the subsequent counselling. I think it was this sort of sentiment that made the Working Party favour a regional rather than a national register. Access to information in the register can, with care, be regulated and limited appropriately; what is much more difficult is to safeguard the interests of those families whose beliefs differ from 'popular' opinion. I believe the tide of prenatal diagnosis is already claiming a few who would have liked to have thought about it longer.

Recommendations of the Clinical Genetics Society Working Party

The Working Party make the following recommendations:

(1) Registers should be set up for the express purpose of tracing, following-up, and counselling individuals who are at high risk (greater than 1 in 10) of transmitting a serious genetic disorder to their offspring. The object is to ensure that such individuals are informed of the risks and the various options available to them.

(2) Registers should be organised on a 'regional' rather than a national basis, and should be located in a regional genetics centre. If registers already exist in units dealing with specific genetic disorders—such as haemophilia—there should be close liaison with the regional genetics centre in order to provide comprehensive facilities for counselling, including risk estimation.

(3) No individuals should be included on the register without their knowledge and approval.

(4) The involvement of family doctors should be sought in every case and encouraged at all stages of contacting, counselling, and follow-up of individuals at risk.

(5) The complexity of the data and the need for co-operation between centres requires a standard form for recording data and an agreed system for coding disease entities. This system should accommodate chromosomal, multifactorial, and unifactorial disorders and should be sufficiently flexible to include newly recognised genetic disorders and possible heterogeneity.

(6) Computerisation of data in a genetic register is recommended for several reasons. It becomes important for ease of storage and retrieval of data (including patient recall) if large numbers are involved. It has the advantage that, with appropriate safeguards, it helps to maintain strict confidentiality. It also provides a facility for fulfilling other functions such as complex risk calculations.

(7) The computer system for a genetic register should ideally have a dedicated minicomputer located in the genetic centre. The main advantages are increased confidentiality and facility of operation. A less satisfactory alternative is a terminal associated with a large central computer.

(8) There should be standardisation of computer equipment and computer programs, both for economic reasons and to facilitate collaboration between different genetic centres. Therefore, it is essential to co-ordinate developments in this field.

(9) The computer program, like all other aspects of the genetic register system, must incorporate strict safeguards for confidentiality.

(10) Access to data in the register must be restricted to certain clearly specified individuals. Personal and medical information should be released only by the clinician in charge of the register.

(11) In establishing a 'regional' genetic register, provision must be made for adequate supporting staff, which might reasonably include a medical geneticist, a clerk/computer operator, and a field worker.

(12) If a general genetic register is not immediately feasible for economic or other reasons, a limited register should be established for specific genetic disorders of particular importance.

It is desirable that there should be as wide a debate as possible both in and outside the profession before these recommendations are implemented in full. Who is going to monitor the success or failure of this important venture?

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Results of a regional cord blood screening programme for detecting neonatal hypothyroidism

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SUMMARY Our regional cord blood screening programme for detecting neonatal hypothyroidism using initial cord blood thyroxine (T4) determinations, with supplemental thyrotropin (TSH), and triiodothyronine resin uptake (T3U) measurements, gave an incidence of thyroid abnormalities of 1/3000 births, with 1/5000 infants having severe primary hypothyroidism. No hypothyroid infant detected in the programme had been suspected clinically before the screening and, in retrospect, only a few babies had any signs of hypothyroidism. Supplemental TSH and T3U determinations were required on 8–12% of the population screened initially with a T4 test to avoid missing affected cases. With an initial T4 and supplementary TSH and T3U testing on cord blood serum, recalls to exclude primary hypothyroidism were reduced to 0·16% of the screened population. The incidence of abnormalities detected in this cord blood screening programme was comparable with that reported by others using neonatal dried blood screening methods, indicating that cord blood screening can be effective provided the appropriate recall criteria and transport conditions are used. Nevertheless, for several practical reasons, neonatal dried blood methods are recommended as the screening test of choice for surveying large populations over extensive geographical areas.

Neonatal hypothyroidism is a condition that may result in mental retardation. Retrospective studies show that treatment before age 3 months lessens the chance of this outcome (Raiti and Newns, 1971; Klein *et al.*, 1972). As it is difficult to make an early clinical diagnosis, laboratory screening programmes have been implemented (Fisher *et al.*, 1976). Cord blood serum TSH alone (Klein *et al.*, 1974), or thyroxine combined with thyrotropin (TSH) (Walfish, 1976), have been used. Alternatively, dried blood spotted on filter paper discs after heel prick at age 3–5 days has been used to measure T4 alone (Dussault *et al.*, 1976), TSH alone (Irie *et al.*, 1975; Illig and Rodriguez deVera Roda, 1976; Larsen *et al.*, 1976; Miyai *et al.*, 1976; Foley *et al.*, 1977), or initial T4 with supplementary TSH (Scriver *et al.*, 1977; Dussault *et al.*, 1978). Neonatal heel prick capillary serum TSH has also been assessed as a screening test (Delange *et al.*, 1977).

To detect neonatal hypothyroidism and lessen the burden of recall in a screening programme using T4 alone (Walfish, 1976), our programme used an initial cord blood serum T4, with selective supplemental TSH and triiodothyronine uptake assays (T3U) to obtain epidemiological data on this disorder in Toronto. The purpose of this report is to summarise the laboratory and clinical data for the 16 infants with confirmed thyroid dysfunction among the 50 000 infants who were tested in this large-scale regional screening programme.

Materials and methods

Cord blood sera and venous samples from patients who were followed up were obtained in a regional screening programme to detect neonatal hypothyroidism. The programme was started in October 1973 at the Mount Sinai Hospital, Toronto, and this was extended to other Toronto Hospitals with approval of the University of Toronto Committee on Human Experimentation.

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Cord blood was obtained after delivery and ligation of the umbilical cord by withdrawing with a syringe 3 to 5 ml venous blood from the placental side. This was stored and taken at 4°C to a central laboratory. After being separated by centrifugation, sera were stored at −20°C until analysis. All assays were performed in duplicate. Using 25 μl serum samples, cord T4 was measured in all infants by a double antibody radioimmunoassay (RIA) technique (Chopra, 1972; Walfish *et al.*, 1973). Each assay 'run', comprising 200–700 samples, was analysed by a histogram and those infants with low T4 values up to either the 8th or 12th centile, depending on the distribution of values, had supplemental duplicate 100 μl serum TSH determinations, using a double antibody RIA (Patel *et al.*, 1971) and duplicate 100 μl serum T3 uptakes with silica talc resin (normal cord serum T3U range relative to pooled control reference was 78 to 110%). Infants in whom the TSH value was >45 μU/ml were followed-up as quickly as possible with additional venous T4, TSH, T3U and, in some cases, total serum triiodothyronine (T3) by RIA (Chopra *et al.*, 1972).

If a persistent abnormality of the thyroid function was noted, the infant was investigated further at the Hospital for Sick Children, Toronto; investigations included repeat serum thyroid function studies, a low dose radioiodine uptake, a technetium thyroid scan, and bone age studies (Greulich and Pyle, 1959).

A low dose (1–2 μCi)^{131}-I uptake was obtained at 2 and 24 hours. This was followed by a technetium 99M rectilinear scan using a 0·5–2 mCi IV dose according to body surface area.

Table 1 gives the nomenclature used.

Results

Thyroid indices on cord blood and at the time of follow-up for the 16 hypothyroid infants are shown in Table 2, including the in-assay location of the cord blood thyroxine value. A summary of the results according to underlying aetiology is shown in Table 3.

The cord blood serum T4 levels in the 16 hypothyroid infants ranged from 2·9 to 8·1 μg/100 ml

Table 1 *Definitions of nomenclature in text*

Cord blood screening parameters			*Final clinical and laboratory diagnoses*
T4 (centile)	*TSH (μU/ml)*	*T3U (%)*	
<12th	>100	Low, N*	Severe primary hypothyroidism
<12th	50–100	Low, N	Other primary hypothyroidism
<12th	<6	Low, N	Secondary hypothyroidism
<12th	<30	High	Hypo-TBG-aemia

*N = normal.

Table 3 *Aetiological classification for the 16 infants with thyroid abnormalities*

	Total
Primary thyroid dysfunction	
Severe primary hypothyroidism	
Athyrosis	4
Enzyme defect (goitrous)	4
Lingual thyroid	3
Other primary hypothyroidism	
Hypoplasia	3
Iodide induced (transient)	1
Secondary hypothyroidism	
Hypothalamic	1

Table 2 *Thyroid indices on cord blood and at follow-up for the 16 hypothyroid infants screened*

Case	*Cord blood*				*Follow-up*			
	T4 (μg/100 ml)	*T4 in-assay location (centile)*	*TSH (μU/ml)*	*T3U (%)*	*T4 (μg/100 ml)*	*TSH (μU/ml)*	*T3U (%)*	*T3(RIA) (ng/100 ml)*
1	6·4	4·2	188	NSQ	2·3	74	68	123
2	7·2	7·6	>96	80	2·6	192	77	NSQ
3	2·9	0·3	300	100	<1	300	86	92
4	3·8	0·6	>96	105	1·8	300	90	50
5	6·9	3·6	192	80	1·9	192	80	NSQ
6	3·8	0·6	128	88	<1	128	81	NSQ
7	3·7	0·4	180	87	3·1	160	81	199
8	3·7	0·3	300	90	2·3	300	71	105
9	7·2	4·9	108	99	5·1	45	95	148
10	4·7	0·3	300	109	1·5	300	84	30
11	3·8	1·4	300	101	<1	300	75	75
12	5·3	3·4	119	87	4·4	47	NSQ	56
13	8·1	8·9	79	100	8·1	66	105	100
14	7·1	11·7	49	104	12·4	40	NSQ	NSQ
15	6·5	4·8	73	76	2·8	126	70	224
16	6·5	4·0	<6	NSQ	4·1	1·4	101	93

NSQ = not sufficient quality (for analysis).
Conversion: traditional units to SI—T4: 1 μg/100 ml ≈ 12·87 nmol/l; T3: 1 ng/ml ≈ 1·536 nmol/l.

(37 to 104 nmol/l), Table 2. The mean ± SD was 5·5 ± 1·7 μg/100 ml (71 ± 22 nmol/l). This was significantly lower by Student's *t* test ($P<0\cdot001$) than the mean T4 of 10·7 μg/100 ml (138 nmol/l) for 4911 normal euthyroid infants previously reported (Walfish, 1976). Eight of the 16 hypothyroid infants had T4 levels within 2 SDs of the normal mean (Table 2). When only those infants with severe primary hypothyroidism (Table 1) are studied, the mean T4 is 4·9 ± 1·6 μg/100 ml (63 ± 21 nmol/l) which is not significantly different from the mean for all the hypothyroid infants. However, those without severe primary hypothyroidism have a mean T4 of 6·7 ± 1·6 μg/100 ml (86 ± 21 nmol/l), significantly higher ($P<0\cdot05$) than for other hypothyroid infants. At follow-up the level of T4 had decreased in all except the 2 infants with hypoplasia.

All infants with primary hypothyroidism had cord TSH >45 μU/ml. Those infants with severe primary hypothyroidism had TSH >100 μU/ml. In all cases (except for the child with secondary hypothyroidism), TSH levels remained >40 μU/ml at the time of the 3–5 week follow-up, when the normal TSH level is less than 10 μU/ml.

Total serum T3 (RIA) was obtained in 11 hypothyroid infants at the time of follow-up and ranged from 30–225 ng/100 ml (0·5–3·4 nmol/l). T3 (RIA) was subnormal (compared with normal adult values) in only 4 of the affected infants and was not a good indicator of hypothyroidism. 14 hypothyroid infants had T3U performed and, in all except one, T3U was within normal limits. Values tended to be parallel to the T4 values, but no infant had a T3U suggestive of primary thyroxine-binding globulin abnormality.

149 (0·3% of the total population) infants have been recalled for suspect primary hypothyroidism. When the number of affected infants is subtracted from the total number recalled and expressed as a percentage, 90% of the recalled infants were proved to be euthyroid at follow-up. 51 infants with T4 in the lowest 12th centile and T3 uptakes >120% were not recalled for suspect hypothyroidism but were followed up, and 8 were shown to have a persistent TBG abnormality. The estimated incidence for our population is therefore 1/6500, which is greater than the incidence previously reported (Dussault *et al.*, 1977) in which direct measurements of TBG were used.

As the TSH assay used in this programme was no more sensitive at its lower limits than 6 μU/ml, it mainly helped to detect primary hypothyroidism. Case 16 was discovered fortuitously to have secondary hypothyroidism, as he was recalled in the early stages of our programme when all infants with low T4 levels were followed up. More recently, those patients with cord serum T4 values in the lowest 12th centile with values below the lower limits of detectability on the supplementary TSH test have not been recalled, and this has reduced the percentage recalled for primary hypothyroidism to 0·16% by excluding follow-up of low T4 infants with low TSH (i.e. possible hypo-TBG-aemia or secondary hypothyroidism).

Clinical studies

Salient data for the 16 infants with thyroid function abnormalities are summarised in Table 4. The babies (9 boys and 7 girls) ranged in gestation from 34 to 42 weeks. Only one (Case 13) had an abnormal birthweight, being low for gestational age. This child had the additional problems of hypospadias, hypoglycaemia, and hypocalcaemia. Follow-up examination was generally between the 14th and 39th day. However, 2 babies in the series were seen later—Case 1 at 80 days, because of a change in her address, and Case 16, who has hypopituitarism, at 308 days, due to reluctance in referral by his doctor. No hypothyroid infant discovered in the screening programme had earlier been suspected to have

Table 4 *Clinical data for the 16 infants with thyroid abnormalities*

Data	*Case*															
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*
Sex	F	M	F	F	M	F	M	M	M	F	F	M	M	F	M	M
Gestation (weeks)	42	40	41	34	38	37	40	34	40	36	39	34	40	40	40	42
Birthweight (g)	4300	3600	3220	1760	3450	2860	3210	2520	3150	2130	2900	2030	1600	2980	3500	3000
Follow-up examination day	80	23	25	33	24	23	31	14	39	27	15	32	28	26	30	308
Length centile	90	90	10	3	10	5	20	3	90	3	10	3	3	10	90	3
Height centile	5	90	75	3	25	5	50	3	75	3	3	3	3	50	75	75
Goitre	–	–	–	–	+	+	+	–	–	–	–	–	–	–	–	–
Clinical hypothyroidism*	+	–	–	+	+	+	–	–	–	+	+	–	–	–	–	+
Bone age (weeks gestation)	38	40	38	36	38	38	36	36	38	38	38	38	40	40	40	38
4-hour radio uptake (9–26%)	2·2	0·5	0	2·0	40	42	33	6·6	3·5	2·0	4	7·4	8·1	5·2	31	ND
Thyroid scan	A	A	A	A	G	G	G	G	L	L	L	H	ND	H	G	ND

* = Criteria of Smith; A = athyrosis; G = goitre; L = lingual; H = hypoplasia; ND = not done;

clinical hypothyroidism. At the initial examination all babies were assessed for hypothyroidism using the criteria of Smith *et al.* (1975). Seven out of 16 had at least one of these criteria; the remaining ones were clinically euthyroid. Three babies had enlarged thyroids, 2 of whom were in the overtly hypothyroid group. The heights and weights of the study group were in the normal range with the exception of 4 premature infants and Case 13. Several babies (Cases 3, 5, 7, 14, and 16) were overweight for their length but only 2 of them were clinically hypothyroid.

Radiological bone age, estimated by the method of Greulich and Pyle (1959), and compared with the age at assessment, was abnormal in 8 of the babies whereas the 24-hour radioiodine uptake was abnormal in all 15. 11 babies had a low uptake, while 3 of the 4 babies with enzyme defects, and the infant with iodine-induced goitre, had increased uptake. Technetium scan detected hypoplastic lingual thyroids in 3 (Cases 9, 10, and 11) and suggested athyrosis in 4 others. The diagnoses made are given in Table 3. 11 infants had significant primary hypothyroidism requiring thyroid replacement with L-thyroxine 5·0–7·5 μg/kg (64–96 nmol/kg) a day. Treatment was started in this group between 15 and 80 days, with a mean starting day of 32, and more recently of 22 days. Case 15, with iodide-induced hypothyroidism, was initially treated with L-thyroxine but his treatment was stopped at age 2 months when the cause was established and he remained euthyroid at subsequent follow-ups. The 3 infants with hypoplasia had subclinical hypothyroidism at reassessment; and 2 were treated with thyroxine replacement but one of these, Case 12, died from sepsis and at necropsy his thyroid gland was shown to be hypoplastic. The family of the one remaining baby in this group, Case 14, elected not to allow treatment, and at age 12 months he was physically and developmentally normal but he still had a raised TSH with normal T4 and T3 levels. Case 16 with hypopituitarism, has hypogonadotropic hypogonadism, and hypothyroidism associated with congenital microcephaly, and moderately severe developmental delay. Thyroid replacement in this child improved his height velocity.

Discussion

This cord blood programme using initial T4 screening with supplemental TSH determination gave a yield of thyroid abnormalities of 1/3000 births with a 1/5000 incidence of severe primary hypothyroidism. This correlates well with the findings of other screening programmes using either cord blood or dried blood spots (Fisher *et al.*, 1976). This is a much greater incidence than that for phenylketonuria (1/16 000) for which screening programmes already exist, and much greater than 1/20 000 estimated from retrospective examination of hospital admissions for cretinism in Toronto (unpublished data). The discrepancy may be caused by early detection of cases that would not have presented with cretinism. However, those cases without athyrosis (i.e. enzyme defect, lingual thyroid, etc.), although biochemically hypothyroid, may in fact not have developed clinical hypothyroidism until later. The particular significance of the 3 cases of hypoplasia is not clear. Such cases may represent either subclinical hypothyroidism or a form of pituitary resistance syndrome where there is a raised serum TSH in the presence of a normal to raised serum T4 concentration (Gershengorn and Weintraub, 1975).

Our programme requires supplementary TSH estimations on the lower 8–12th centile of the T4 'run'. This high incidence of supplemental TSH determination using cord blood serum is necessary because T4 levels may be low in premature infants, twins, and in other euthyroid infants (Walfish, 1976; Ginsberg *et al.*, 1978). The technical and clinical problems that could arise from using an absolute value of T4 for determining which samples have supplemental TSH testing within a screening programme has previously been discussed (Walfish, 1976). As the cord serum T4 was within the 95th centile of the normal population for most of the affected hypothyroid infants, we feel it is necessary to take a relatively large number of infant samples for supplemental TSH estimations to avoid the possibility of missing a hypothyroid infant. Similarly, a hypothyroid infant with cord serum T4 values above the lower 2·5th centile of the normal general population has been reported (Klein *et al.*, 1976). Because of its relative nonspecificity and the high recall burden imposed by screening for T4 alone, it is not recommended as the only screening technique (Walfish, 1976; Scriver *et al.*, 1977; Dussault, *et al.* 1978).

Several high false-positive TSH values were seen secondary to extreme parturition stress (Walfish, 1976; Delange *et al.*, 1977). No false-negative results have so far been seen as all infants with primary hypothyroidism had TSH values >45 μU/ml, and those with very significant primary hypothyroidism had values >100 μU/ml. As stated earlier, TSH is the single most specific test for detecting infants with primary hypothyroidism. Because of the cost of reagents and the need for technical expertise (and the inability to detect secondary hypothyroidism or TBG abnormalities), we have not advocated a TSH test as the only screening method. However, if one wanted to rely on a single test to detect primary hypothyroidism, TSH screening would seem to be the most appropriate. So far our programme, using an initial T4 with a supplementary TSH and T3U test on cord blood serum, has decreased the number of patients needed to be followed up for primary neonatal hypothyroidism to an acceptable 0·16% of the total population. If a cord blood sample is not received, then a dried blood heel prick spot is obtained at between 3 and 5 days and initial T4 and supplementary TSH tests performed. To our knowledge, no infant with primary hypothyroidism has failed to be detected (i.e. no false-negative results).

The clinical and laboratory data recorded here are somewhat at variance with those in current texts. Rather than showing a female preponderance (Carr *et al.*, 1961; Andersen, 1969), the sex ratio is equal, but the small number of subjects may be the reason for this. Fewer than half of the cases showed any criterion of hypothyroidism using the parameters of Smith (Smith *et al.*, 1975). This finding is in direct contrast to that of Guyda *et al.* (1977), but it is in agreement with the data of others; Klein *et al.* (1976) found little clinical evidence of hypothyroidism among their detected infants. In contrast to other reports (Smith *et al.*, 1957, 1975), delayed radiological bone age, as an index of skeletal maturation, did not correlate well with hypothyroidism in our series.

While awaiting the results of the hormone assay, a low dose 24-hour radioiodine thyroid uptake was performed and, if this was abnormal, replacement therapy could be begun. Technetium scanning allowed the defect in the thyroid to be estimated so that appropriate genetic counselling could be given to the parents. A low dose ^{131}-I uptake procedure was routinely performed but the technetium 99M scan could be used instead for the anatomical localisation of the thyroid gland abnormality with less radiation exposure. Nevertheless, information on goitrous lesions and their underlying biosynthetic defects can be obtained from radioiodine studies (^{123}-I preferably if available) at negligible radiation risk if the appropriate low doses are used.

The distribution of diagnoses in this small number of cases differs from that in previous reports in which it is suggested that most cretins have athyrosis (Wilkins, 1960; Carr *et al.*, 1961). In our group only 30% were athyrotic, 30% had enzyme defects, and 20% lingual glands. This distribution is similar to that found by others (Andersen, 1966) from an analysis of congenital hypothyroidism based on radioiodine thyroid uptake.

Cord blood serum is easy to obtained, it can be handled easily, and it requires less cumbersome radioimmunoassay procedures for T4 and TSH than the dried blood spot. Excess serum is also readily available for repeat analyses and for T3U tests for determining abnormal thyroid hormone protein binding. The main difficulty with such a method is that the sample has to be sent to a central laboratory and then isolated from other inborn error screening tests. Dried blood placed on filter paper is an alternative method and has the advantage that it can be transported over wide areas (Fisher *et al.*, 1976; Scriver, 1977; Dussault *et al.*, 1978). Such a technique may be combined with screening for phenylketonuria and with other inborn error screening programmes that can be assayed from neonatal dried blood filter paper discs (Scriver *et al.*, 1977). However, assays performed from dried blood filter paper discs require proper collection and saturation of both surfaces of the filter paper (Walfish, 1975), and there is the risk of blood TSH instability and a significant reduction in measurable TSH activity within several weeks at high ambient temperatures (Naruse, 1978; P. G. Walfish, 1979, in preparation) such as may occur if they are sent by post. The estimated cost for the cord blood screening programmes as described, using initial cord blood serum T4 determinations with supplementary TSH and T3U assays is $1.50 per infant excluding overhead and capital equipment expenditures, but other dried blood programmes have reported similar or lower costs (Fisher *et al.*, 1976).

Regardless of whether cord blood serum or neonatal dried blood is used, screening programmes for neonatal hypothyroidism will find it difficult to detect infants with secondary hypothyroidism (low T4 with low TSH) who reportedly represent between 6 and 10% of the total neonatal hypothyroid population (Fisher *et al.*, 1976; Dussault *et al.*, 1978). However, the low incidence of secondary hypothyroidism, its difficulty of detection, and the overlap with normal infants having low TSH values will require an unusually high burden of recall of over 1% of the population surveyed (Dussault *et al.*, 1978) in order to detect such cases; this is a known limitation of any screening programme regardless of method, owing to the poor discrimination between infants with low TSH secondary hypothyroidism, those with low TSH of congenital hypo-TBG, and normal infants. Our programme has therefore recently been altered to screen only for primary neonatal hypothyroidism and this has further reduced the number recalled to 0·16%.

Despite these limitations, the high incidence of thyroid abnormalities detected by cord blood screening has shown that this approach may be as effective as neonatal dried blood screening methods in detecting neonatal hypothyroidism if the appropriate recall criteria and transport conditions are used. This study shows that cord blood serum screening was successful in detecting neonatal hypothyroidism within densely concentrated population areas with high birth rates, provided that a central assay laboratory is available to optimise quality control and to reduce administrative costs. Nevertheless, owing to the practical considerations, and in agreement with previous reports (Fisher *et al.*, 1976; Scriver *et al.*, 1977), we recommend the neonatal dried blood collection method as the screening test of choice when surveying large populations over extensive geographical regions.

Although supported by retrospective studies (Raiti and Newns, 1971; Klein *et al.*, 1972), the value of prompt detection and early thyroxine replacement remains to be assessed prospectively, in our cases of primary hypothyroidism. It is too soon to assess accurately the intellectual development for these infants, but at present all primary cases appear to be growing at a normal velocity and have normal motor milestones, suggesting that early detection and therapy have been of significant value.

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Response of term babies to a warm environment

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SUMMARY The response of healthy term babies to warm environments was assessed by placing them naked in incubators and increasing the air temperature in steps until either sweating occurred or the rectal temperature reached 37·9°C. The rate of evaporation of water from the skin was measured by a method based on the estimation of vapour pressure gradient. When a 50% increase in the rate occurred at a given site, sweating was judged to have begun. 39 studies were made on 30 babies, aged from 4 hours to 11 days. As babies approached the point of sweating, spontaneous activity usually ceased, the skin reddened, and a sunbathing posture was adopted. Sweating was found on 35 occasions. It was most pronounced and often was found initially on the forehead but it was also detected on the trunk and limbs. No thermal sweating was noted on the palms or soles. Sweating generally began when the incubator air temperature exceeded 34°C and the rectal temperature exceeded 37·1°C, but there was wide individual variation. Older and more mature babies tended to sweat at lower air temperatures.

Sweating is man's most important defence against overheating. It is highly developed in the heat-acclimatised adult who can lose over a litre of water an hour by this route, an evaporative heat loss of 700 W. Before sweating occurs, skin blood flow is increased which raises skin temperature and increases heat loss by radiation and convection. By these adjustments adults are able to maintain deep body temperatures within a narrow range in high environmental temperatures. Very few investigations have been made on the response of the newborn baby to high ambient temperatures. By virtue of his size the newborn in the company of adults is more at risk of cold exposure. However, the clinical emphasis on the importance of keeping babies warm has led to the introduction of powerful heating devices, such as incubators and radiant warmers, into routine service and with this has come the risk of overheating. Just as it is important to know the ambient temperatures at which babies of different ages, sizes, and gestations switch on thermogenesis thus increasing their need for oxygen and substrate, so it is important to know the ambient temperatures at which they are likely to begin to sweat and thus increase their need for water.

A simple method for measuring evaporative water loss from the skin is available (Nilsson, 1977). We used this in combination with measurements of skin temperature to study the range of responses of the healthy term baby to high environmental temperatures.

Method

Rates of evaporation of water from the skin were measured with the Evaporimeter EP1 (Servomed), a method based on estimation of the water vapour pressure gradient close to the skin's surface. The technical details have been reported by Nilsson (1977).

Each baby after a feed was placed naked on his back inside an incubator (Vickers 79). The air temperature of the incubator was set near the lower point of the thermoneutral range according to the values reported by Hey (1971). The probe of the Evaporimeter was placed lightly on the baby's skin until a stable reading of evaporation rate was obtained. Measurements were made at 11 defined skin sites on each baby: forehead, cheek, chest, abdomen, anterior upper arm and forearm, palm, anterior thigh and lower leg, dorsum of the foot and sole. These sites were chosen so that the infant lying on his back was not disturbed. At the same

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time, the following temperatures were measured by thermocouple: air temperature in the centre of the incubator, skin temperature of the upper abdomen and dorsum of the hand by lightly taping the thermocouple to the skin, and rectal temperature, with a probe inserted about 8 cm into the baby's rectum.

30 minutes were allowed for the infant to adjust to any change in environmental conditions. After the initial readings were made, the incubator air temperature was increased in steps of 0·5–1·5°C. 30 minutes later, evaporation rates and temperatures were recorded before the incubator air temperature was again increased, and this sequence was continued until the baby began to sweat or until his rectal temperature reached 37·9°C. This is the average body temperature of babies before birth (Mann, 1968). As sweating is influenced by exercise as well as by temperature, measurements were not made on active or crying babies. In this study sweating was defined as an increase in evaporation rate of at least 50% above the initial rate of water loss from that skin site. In most cases the increase was considerably greater, in some instances 10 to 18 times higher than the initial values. The upper critical temperature of the thermoneutral range is usually defined as that environmental temperature at which sweating first occurs. As the incubator air temperature was increased in steps, the upper critical temperature for each baby was somewhere between the air temperature at which sweating did not occur and the air temperature at which it did. Because this point was not accurately defined, we have expressed all our results in terms of the incubator air temperature at which sweating was first detected. This temperature is not the operative environmental temperature because no allowances were made for radiant heat exchange between the baby and the inner surface of the single-walled incubator. The average room temperature was 27·2°C (range 24·9–29·9°C). Thus the operative environmental temperature was likely to be about 1°C lower than the actual incubator air temperature (Hey and Mount, 1966). The relative humidity inside the incubator was not controlled but it was measured. It varied between 26 and 58%.

39 studies were made on 32 healthy term babies. Gestational age was calculated in completed weeks of pregnancy from the first day of the mother's last menstrual period. It ranged from 37 to 42 weeks (mean 39·7). Birthweight ranged from 2·77 to 4·70 kg (mean 3·43). The age of the baby varied from 4 hours to 11 days. Each study was made with the full informed consent of the mother, usually in her presence, and the investigation was approved by the North Nottinghamshire Health District Ethical Committee.

Results

The results of a typical series of observations are illustrated in Fig. 1. With each increment in incubator air temperature, the peripheral temperature on the dorsum of the hand rose sharply. Abdominal skin and rectal temperatures also rose, but at a slower rate. After 30 min at an incubator air temperature of 36·6°C, when the peripheral and abdominal skin temperatures were the same and the difference between skin and rectal temperature was only 0·5°C, the baby began to sweat.

The incubator temperatures were never raised so that the infant's rectal temperature exceeded 37·9°C. With this limitation, sweating was detected in 35 out of the 39 studies. On 11 occasions sweating was only noted on the forehead. On 14 occasions it occurred on the forehead first and only appeared elsewhere when the air temperature was further raised. It then progressed to the chest, arms, abdomen, and legs, usually in that sequence. On the remaining 10 occasions, sweating was noted at several sites simultaneously, always including the forehead. The mean rates of evaporation of water at the different sites, initially and after sweating occurred, are shown in the Table. Sweating was most pronounced on the forehead.

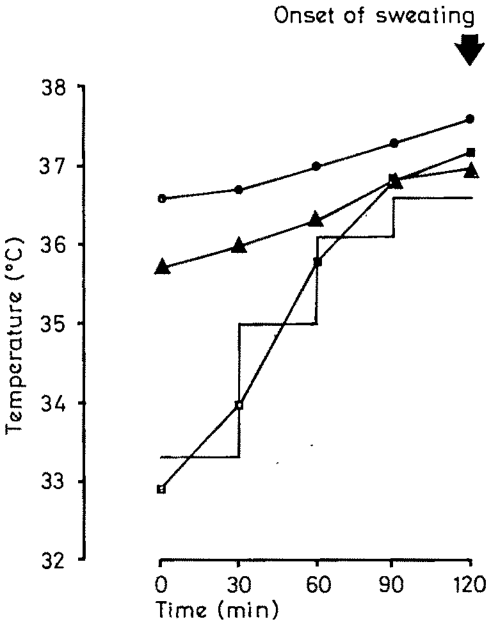

Fig. 1 *The effect of step-wise increases in the incubator temperature (——) on body temperatures (● rectal, ▲ abdominal skin, ■ hand) of a naked, term infant, birthweight 2·95 kg, age 21 hours. The arrow head indicates when sweating began.*

Table *Mean rates of evaporation from different skin sites in 39 babies. Initial rates were obtained after the baby had been naked in an incubator for 30 min at a temperature near the lower end of the thermoneutral range. Sweating was judged to have occurred when, after increasing the ambient temperature, the evaporation rate increased by at least 50% above the initial value*

Skin site	*Mean initial evaporation rate (g/m² per hour)*	*Mean maximum evaporation rate when sweating (g/m² per hour)*	*No. of times sweating detected (no. of studies = 39)*
Forehead	6·2	52·6	35
Cheek	8·2	16·2	13
Chest	4·8	16·7	21
Abdomen	4·9	11·3	15
Upper arm	5·6	12·5	14
Forearm	5·2	15·3	18
Palm	14·6	—	0
Thigh	5·4	12·3	11
Lower leg	4·9	11·8	12
Foot—dorsum	4·6	13·2	7
Foot—sole	9·6	—	0

There were wide variations in the incubator air temperatures, the rectal temperatures, and the abdominal skin temperatures at which sweating was first detected (Fig. 2). There was a significant trend for infants of longer gestations to sweat at lower ambient temperatures but there was no obvious difference in the skin and rectal temperatures at which sweating first occurred in the more mature babies (Fig. 3). Infants who were at least 6 days old, sweated at significantly lower ambient temperatures than infants in the first 4 days of life, but again no change in the skin and rectal temperatures when sweating occurred was noted as the postnatal age increased (Fig. 4). Four infants were studied serially during the first week of life. In all 4 the air temperature at which sweating was first observed fell by 1·3–2·6°C. The relative humidity of the incubator air, in the range of 26–58%, did not appear to influence the ambient temperature at which sweating first occurred.

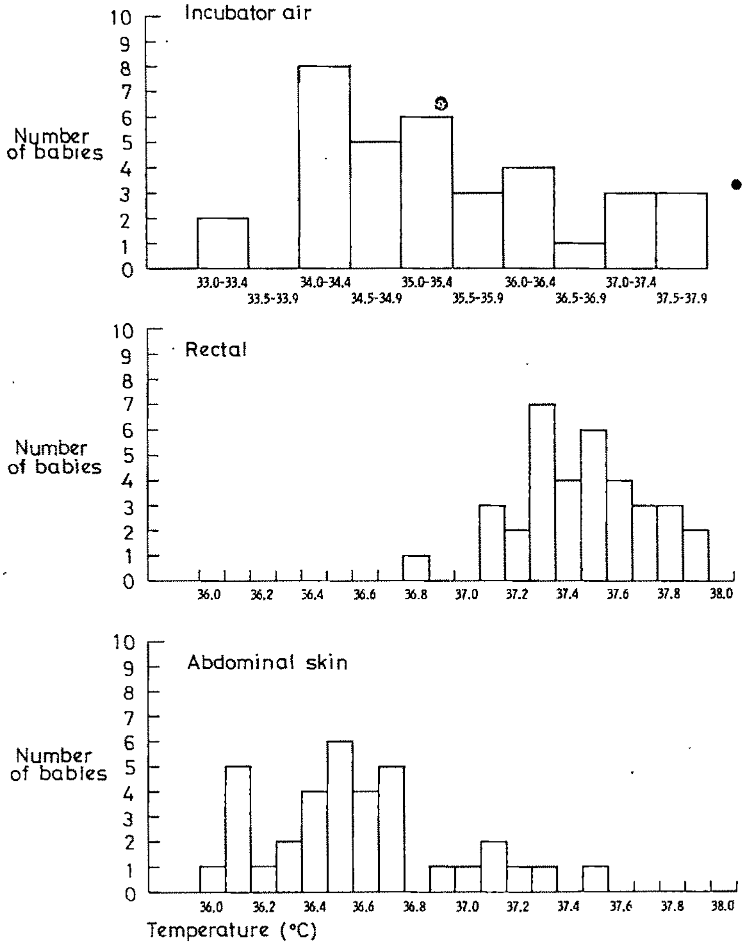

Fig. 2 *Temperatures of the incubator air, rectum, and abdominal skin at which sweating was first detected in 35 infants.*

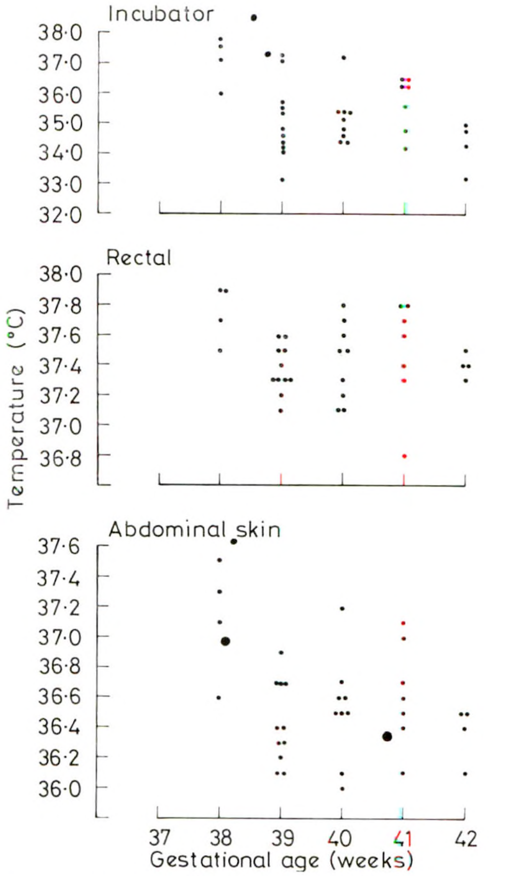

Fig. 3 *Relationship between gestational age and the incubator air, rectal, and abdominal skin temperatures at which sweating first occurred. The more mature infants began to sweat at lower incubator air temperatures* (*P* = *0·05*).

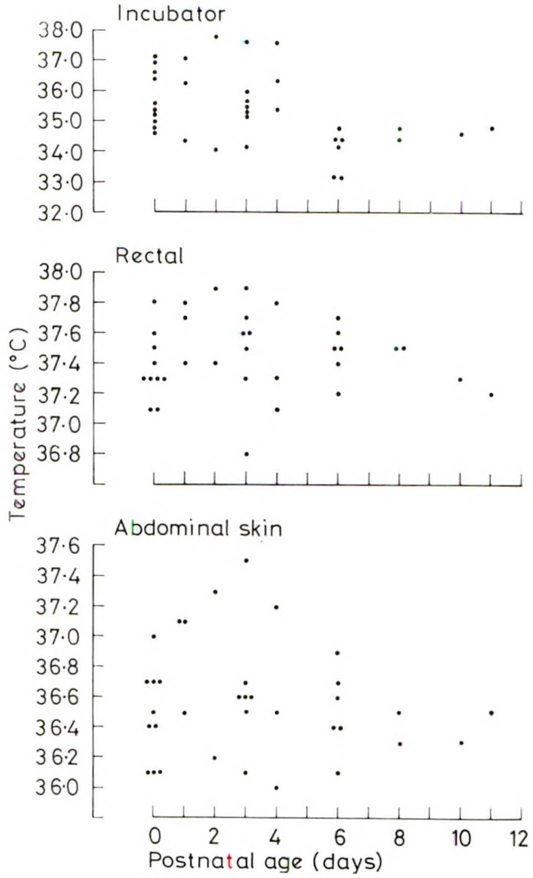

Fig. 4 *Relationship between postnatal age and the incubator air, rectal, and abdominal skin temperatures at which sweating first occurred. Babies aged 6 days or more, sweat at significantly lower air temperatures than those aged 4 days or less* (*P* = *0·01*).

In the infants who did sweat, sweating occurred when the peripheral and abdominal skin temperatures were similar and the rectal and skin temperatures differed by about 0·5°C. In the 4 infants who did not sweat, these conditions were reached and all the measured temperatures then rose with each upward step in ambient temperature without detectable sweating (Fig. 5).

In a few instances, sweat was visible on the forehead when rates of sweating were very high but usually it was not seen. Certainly the onset of sweating could not be detected visually. However, the infants did make consistent responses to the increasing ambient temperature. As the air temperature rose the skin colour reddened, spontaneous movements diminished, and when sweating began the infants assumed the posture of a sunbathing adult, lying supine with arms and legs outstretched (Fig. 6). No panting was observed.

Discussion

Sweat response. We have demonstrated that term babies are able to sweat and that sweating readily occurs on the first day of life. This was not found by Uchino (cited by Kuno, 1956) who measured water loss from the chest only, but it was reported by Hey and Katz (1969) who measured total evaporative water loss in a metabolic chamber. We cannot explain why 4 babies did not sweat in spite of high rectal temperatures, although 2 were shown on a later occasion to be able to do so. We found that

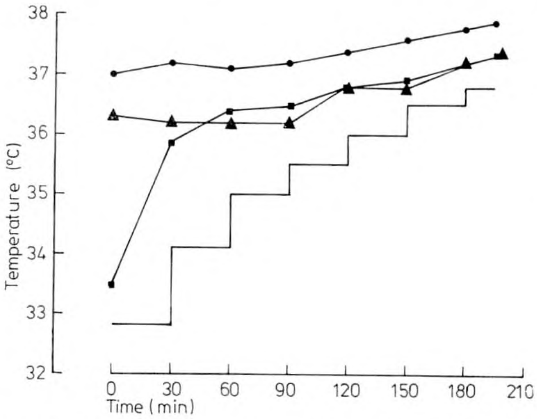

Fig. 5 *The effect of step-wise increases in the incubator temperature (——) on body temperatures (● rectal, ▲ abdominal skin, ■ hand) of a baby in whom no sweating was detected. The baby was born at 37 weeks' gestation, weighing 3·41 kg, and was 6 days old when studied.*

the forehead was the earliest site at which sweating occurred, that it was usually most intense there, and that it was sometimes the only site where a sweat response was detected. We chose the centre of the forehead because it was a convenient site for measurement but sweating of similar intensity was found simultaneously on the temples, behind the ears, and over the occiput but sparing the top of the scalp. Sweating on the forehead of the newborn infant was observed by Foster *et al.* (1969); they pointed out that the sweat glands at this site are the first to develop in fetal life. When progression of sweating occurred, the order from head to chest, arms, abdomen, and legs was similar to that described in adults (Rothman, 1954). Furthermore the relative intensity of sweating at the different sites is similar to adults (Kuno, 1934), but absolute values are generally lower. It must be pointed out however, that we did not attempt to press the infants to their maximum possible rates of sweating. Hey and Katz (1969) found that evaporative water loss per unit area is lower in the sweating baby than the sweating adult. The high initial rates of water loss from the palms and soles which did not change as ambient temperature increased were noted in adults by Kuno (1934). Perpetual sweating is thought to occur at these sites and cannot be abolished by cooling; described as emotional or mental sweating, it can be induced in an adult by mental arithmetic or anxiety.

Both gestational age and postnatal age influenced the environmental temperature at which sweating occurred but there was much individual variation. Many factors are likely to be involved, including maturation of control systems, variations in thermal insulation, and differences in resting metabolic rates. The charts of Hey (1971) suggest that term babies nursed naked in incubators do not greatly increase their evaporative water loss until the operative environmental temperature reaches about 34°C on the first day or 33°C at about 10 days of age. Our results are generally consistent with these observations, as only a few babies sweated at temperatures below these and most babies did so at temperatures 0·5–1·0°C higher. The fall in incubator air temperature at which sweating first occurred as postnatal age increased was independent of gestational age. It mirrors the rise in resting metabolic rate which

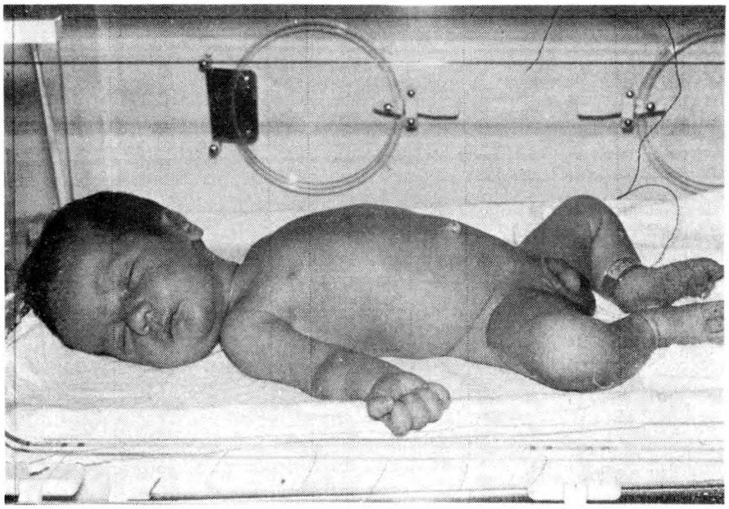

Fig. 6 *Typical sunbathing posture of a sweating baby.*

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Medulloblastoma—a changing prognosis?

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SUMMARY 87 of 90 consecutive cases of medulloblastoma diagnosed at The Hospital for Sick Children, London, in the 10-year period 1965–74 were followed-up until death or until 1 January 1978. Only one patient survived in the 1st 5-year period and is a cure. In the 2nd 5-year period 17 (41 %) of 41 patients presenting are alive and, of these, 11 are 5-year survivors (= 39 % of possible 5-year survivors). Reasons for this improvement are discussed; it is thought likely that the main contribution is improved radiotherapeutic techniques.

Since Bailey and Cushing established medulloblastoma as an entity in 1925, it has been regarded as a predominantly paediatric cerebral tumour with a poor prognosis. Cushing (1930) showed that survival with radical surgery alone was impossible so that the current mainstays of treatment are a combination of surgery and radiotherapy. Surgery to the posterior fossa is as radical as is allowed at operation, and is followed by radiotherapy to the whole craniospinal axis as seeding occurs through cerebrospinal fluid paths. Until the 1950s very poor survival rates were uniformly reported (e.g. Lampe and MacIntyre, 1949; Chatty and Earle, 1971), but since then prognosis has improved, almost certainly because of better radiotherapeutic techniques (Smith *et al.*, 1961; Bloom *et al.*, 1969; Hope-Stone, 1970). Five-year survival rates as high as 75 % have been quoted (Hope-Stone, 1970) but to the family doctor or neurosurgical unit counselling the newly diagnosed patient, the outlook is confusing as survival is generally quoted after successful completion of treatment. We report the follow-up on 87 of 90 consecutive cases diagnosed in the 10 years 1965–74. Histology in each case was confirmed by Professor T. Crawford at St George's Hospital. Divided into two consecutive 5-year periods there is more than a suggestion that the survival in the 2nd is better.

Cases and methods

Of 90 consecutive cases diagnosed with medulloblastoma in the 10-year period 1965–74, all except 3 cases have complete follow-up. These 3 (described below) are excluded from all the discussion.

Cases lost to follow-up.

Case 1
Girl, complete removal at diagnosis July 1967. Received no radiotherapy or other treatment. No details available since December 1973, when in Malta, alive and well; therefore 6 years after craniotomy, well.

Case 2
Boy, partial surgical removal in November 1969 followed by 5000 rads tumour dose to posterior fossa and 3000 rads to cranium and spinal cord. 14 months after treatment in Qatar in March 1971, said to be blind but otherwise well. No further details.

Case 3
Girl, diagnosed February 1970. Partial removal followed by suboptimal cranial irradiation (3000 rads) and no spinal irradiation. Two months after operation had the insertion of a ventriculo-atrial shunt and was then lost to follow-up in Iran in June 1970.

Cases 2 and 3 have possibly died, but Case 1 is a 'long-term' survivor.

Cases with complete data.

Sex
52 boys and 35 girls.

Age
Three months to 11 years, median 4 years.

Length of symptoms before diagnosis
One week to greater than one year, median < 3 months.

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Symptoms

These were well described recently by Gjerris (1976). Symptoms of many of the cases in this series were discussed previously by Till (1975).

Surgery

Definitive surgery was carried out in 94% of cases at The Hospital for Sick Children in London. As a routine this consisted of posterior fossa decompression with removal of as much tumour as the surgeon considered possible at the time of operation. Macroscopic removal was thought complete in 9 (10%) cases and partial in 72 (83%). In all except one, surgery was at the time of initial diagnosis, the exception being a patient referred from Zambia who had received 4 months of chemotherapy (prednisolone, methotrexate, and vincristine) before transfer to England for surgery. Of the 5 cases not receiving definitive surgery, 3 were preoperative deaths and 2 presented with spinal secondaries for which they had laminectomies; one of these 11 months later had a frontal craniotomy for a frontal secondary.

Radiotherapy

11 of 87 patients died before radiotherapy could be initiated, and 2 other patients were not given radiotherapy. Five patients died during radiotherapy. Thus 66 (76%) patients survived the combined treatment of surgery and radiotherapy. Radiotherapy was carried out at 6 different centres—38 cases were treated at UCH, London, receiving treatment with 250 kV equipment until 1967 and subsequently with ^{60}Co equipment. 12 cases were treated at Guildford, before 1968, receiving radiation from 250 kV equipment. 13 cases received treatment at the Royal Marsden Hospital, 3 before 1968 using 250 kV equipment, and 9 after 1968 using 6 MeV equipment. One case was treated at Northampton, one at Nottingham, and one at Derby. Before 1968, radiotherapy was generally with 250 kV equipment and after this date with ^{60}Co or 6 MeV equipment.

Radiation dosage varied, particularly before 1970. The overall outcome of the 87 cases presenting is shown in the Figure.

Table 1 shows how the dosage of radiotherapy has on the whole increased at the various centres in the 2nd 5-year period. Other features of radiotherapy technique have changed. In addition to greater total radiation dosage, better care has evolved by firstly avoiding areas of underdosage of the neuraxis which might allow seeding of tumour cells, and secondly by ensuring no overlap of spinal and cranial fields which might lead to gliosis at the junction of these.

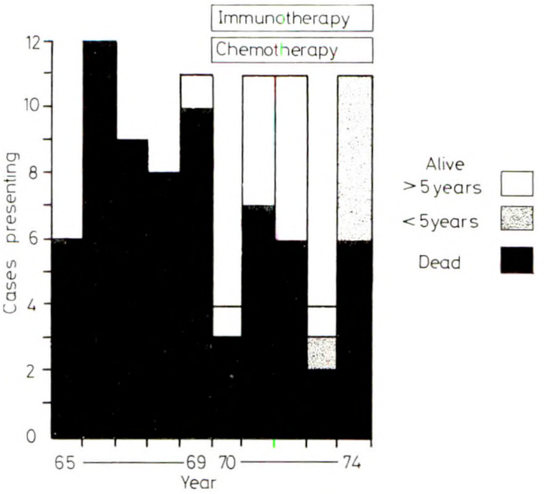

Figure *Outcome on 1 January 1978 for all cases according to year of presentation.*

Table 1 *Dosage of radiotherapy given*

		Adequate treatment	
Period	*Total no.*	*Posterior fossa**	*Spinal cord†*
1965–69	33	10	13
1970–74	33	30	28
		P<0·001	P<0·001

*Adequate treatment posterior fossa = >4000 rads, †spinal cord = >3000 rads.

Immunotherapy (Bloom, 1975)

After 1970 immunotherapy was given to 14 patients as part of a wider trial. Active immunisation was attempted, using autologous medulloblastoma tissue irradiated with 15 000 rads and injected postoperatively subcutaneously. Six injections were normally given during the course of radiotherapy. Seven of these 14 patients are alive, and all are 5-year survivors.

Chemotherapy

12 patients received chemotherapy with their initial treatment and 2 received chemotherapy with recurrence. One case from Zambia had chemotherapy before surgery (see above). The type of chemotherapy varied from one injection of vincristine only to a combination of intrathecal methotrexate, oral CCNU, and IV vincristine in repeated courses. No cases included in the co-operative European trial of adjuvant chemotherapy run by the International Society of Paediatric Oncology (SIOP), which started in January 1975, are included in this series which is complete up to the time of the start of the trial.

Results

The overall outcome of the 87 cases presenting is shown in the Figure. The age range, sex ratio, and length of symptoms before diagnosis are all similar to other extensive series. All except one case diagnosed in the 1st 5-year period died within 4 years, the exception being alive and well 9 years after operation. In the 2nd 5-year period 11 cases are 5-year survivors (39% of those possible), and 6 others are alive and well, although they are not yet 5-year survivors.

All 18 of the current survivors received surgery followed by 5000 rads to the posterior fossa, and 3000–3500 rads to the spinal cord. Seven cases in addition had immunotherapy and 7 chemotherapy. Should complete surgical removal of macroscopic tumour be possible, prognosis is better, 55% are survivors compared with 18% of the partial removal group (χ^2 $P<0{\cdot}01$).

Five survivors are completely well and asymptomatic. Four have features possibly referable to their surgery or radiotherapy, such as visual loss or short stature, and 6 have soft signs such as mild ataxia which could be due to initial tumour damage, surgery, or radiotherapy. Two survivors have severe clinical problems interfering with their everyday life, and both of these have evidence of tumour recurrence.

Two patients presented with secondaries at the time of diagnosis—both are dead. One patient without shunt finally died with extracerebrospinal secondaries in the lung. Secondaries outside the central nervous system are well recorded although rare with this tumour but have never before been recorded within the lung in the absence of a ventriculo-atrial shunt (Makeever and King, 1966).

Table 2 compares the outcome in the two 5-year periods 1965–69, 1970–74. It considers both the total cases presenting and the prognosis in those successfully completing surgery and radiotherapy. The 5-year survival of all cases presenting has improved from 2% in the first period to 39% of those cases in the 2nd period where 5-year follow-up is so far possible. By the χ^2 test these differences are statistically highly significant.

Table 2 *Comparison of survival in the two periods 1965–69 and 1970–74*

Outcome	*Period*	*No.*	*Survival*	
			2 years	*5 years*
			No. (%)	*No.* (%)
Cases presenting	1965–69	46	6 (13)	1 (2)
	1970–74	41	22 (53)*	11 of 28 so far (39)*
Cases completing radiotherapy	1965–69	33	6 (19)	1 (3)
	1970–74	33	22 (65)	11 of 23 so far (48)*

*χ^2 $P<0{\cdot}001$.

Discussion

Cushing, having defined medulloblastoma as an entity, recognised two things about this tumour. Firstly, that there was a high operative mortality and secondly, that without additional radiation, death was invariable within 6 months of diagnosis. The high operative mortality has been confirmed more recently (Smith *et al.*, 1961; McFarland *et al.*, 1969). Elsberg and Gotten (1933) showed that a more conservative approach to surgery consisting of decompression of the posterior fossa with removal of the bulk of tumour tissue and reopening of cerebrospinal fluid paths, gave much better operative figures and did not appear adversely to influence the long-term outcome. This approach, probably associated with advances in anaesthesia and intensive postoperative care, has improved operative and immediate postoperative mortality in this series to 14% (20·5% of the 1st 5-year group and 10·0% of the 2nd group).

The improved survival in the 2nd 5-year period is shown in Table 2. In addition to surgical advances, this improvement could be due to other factors. Firstly, radiation therapy techniques improved in this period with the change from 250 kV to 2–10 MeV or ^{60}Co equipment (Bloom *et al.*, 1969). Secondly, a higher dosage of radiotherapy was applied to both posterior fossa and spinal cord (Table 1) and with awareness was probably applied more effectively. Thirdly, immunotherapy or chemotherapy may have improved the outlook. Because 4 of the survivors had only surgery and radiotherapy, it is likely that improved prognosis is due mainly to improved radiotherapy, not to chemotherapy. This is substantiated by data from the first 100 patients on the SIOP trial of adjuvant chemotherapy in medulloblastoma, where so far there is no difference between patients allocated chemotherapy in addition, compared with the group receiving surgery and radiotherapy alone (Bloom, 1977, personal communication). However, this trial has only been in effect 3 years, so it is too early to draw any conclusions.

The improved techniques of radiotherapy have been described (Smith *et al.*, 1961; Bloom *et al.*, 1969; Hope-Stone, 1970). Hope-Stone in a series of 35 cases, had a 58% 5-year survival but only in a group completing successfully surgery and radiotherapy. The mean age in this series was 9 years which is old compared with other series, and this may favourably have influenced his results.

The reason for the poor survival in the first 5-year period has to be attributed to inadequate radiation, as overall only cases receiving 5000 rads to posterior fossa and 3500 rads to the spinal cord survived. Very few cases in this group received this amount of radiation (Table 1).

For the paediatrician or neurosurgeon counselling parents at the time of diagnosis, it is important to know that the prognosis is improving. At least 39% are now 5-year survivors and overall in this series, no patient has died more than 4 years after diagnosis, although late deaths have occurred in other series (Gjerris, 1976). It may be that 5-year survival will be as high as 46%. By the age + 9 months rule (Collins rule for embryonal tumours) we have overall in the 10-year period 7 (8%) cases cured of their condition (Bloom *et al.*, 1969).

My thanks for encouragement and information from Mr Kenneth Till and Mr Norman Grant, The Hospital for Sick Children, London, Dr Nicholas Godlee and Dr Robert Boyd, University College Hospital, London, Dr H. J. G. Bloom, Royal Marsden Hospital, London, and many other paediatricians.

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A controlled trial of cyclophosphamide and azathioprine in Nigerian children with the nephrotic syndrome and poorly selective proteinuria

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SUMMARY In a controlled trial, symptomatic treatment alone, or 12 weeks of cyclophosphamide or azathioprine were compared in Nigerian children with nephrotic syndrome (mainly quartan malarial nephropathy) and poorly selective proteinuria. Full remission in 2 patients in each of the two groups treated with drugs, and diminution of proteinuria in most patients in the cyclophosphamide group showed possible evidence of benefit. Infections during treatment were significantly more common in the drug-treated groups but were controllable. Mortality from renal failure in the 2nd year after treatment was significantly greater in the azathioprine-treated group than in the other two, suggesting that the drug may have exacerbated the nephritis. The 5-year survival rate was similar in the cyclophosphamide and the control group.

Nephrotic syndrome is common in Nigerian children and in most the disease is associated with *Plasmodium malariae* infection (Hendrickse and Gilles, 1963). Renal biopsies show an unusual type of glomerulonephritis (Hendrickse *et al.*, 1972) which is associated with deposition of immunoglobulin, complement, and malarial antigen in the kidney (Houba *et al.*, 1970; Hendrickse *et al.*, 1972). Most such patients do not respond to corticosteroid drugs and may be made worse by them (Hendrickse *et al.*, 1972). A corticosteroid-responsive minority is to be found among cases with less severe renal biopsy abnormality and highly selective proteinuria (Hendrickse *et al.*, 1972; Adeniyi *et al.*, 1976). No effective treatment is yet available for most patients and mortality is high.

Immunosuppressive treatment has been widely used in nephritis but controlled evidence of benefit is available only for corticosteroid-responsive nephrotic syndrome and SLE nephritis. Spontaneous recovery occurs in almost all kinds of nephritis. All the drugs used are toxic and increase susceptibility to infections; this is a serious problem in malnourished communities with poor sanitation.

It has been suggested that susceptibility to nephritis may result from defective antigen elimination because of relative immunodeficiency (Soothill and Steward, 1971). Hence although immunosuppressive treatment may be valuable if it affects the damaging mechanism more than the elimination of antigen, it may make the nephritis worse if the reverse is true. We therefore assessed the effect on Nigerian nephrotic children with poorly selective proteinuria of a standard regimen alone, or with cyclophosphamide or azathioprine (randomly allocated), on proteinuria, survival, and incidence of complications.

Patients and methods

Children with nephrotic syndrome (oedema, heavy proteinuria, and serum albumin <20 g/l) who presented sequentially at this hospital in Ibadan with nephrotic syndrome were divided into one of two groups according to differential protein clearance; those with highly selective proteinuria were included in a study of corticosteroid response (Adeniyi *et al.*, 1976).

The present study was on 36 children (23 boys and 13 girls) aged between 2 and 12 years who had poorly selective proteinuria, clearance of IgG over clearance of albumin (CG/CA) >15%.

The patients were randomly allocated. Each drew a sealed card from a box, giving the name of one of

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the three groups—azathioprine, cyclophosphamide, or control. Cyclophosphamide was given orally as a single daily dose of 3 mg/kg per day for 12 weeks and azathioprine 2·5–3 mg/kg per day similarly for 12 weeks. Haemoglobin, packed cell volume (PCV), white blood count (WBC), platelet counts, and differential protein clearance were done on all patients before starting treatment; a renal biopsy was done before treatment started in most of them.

Proteinuria was detected in urine by Albustix, and was graded O, ±, + to 4 + according to the manufacturer's scale. Differential protein clearance studies were performed on random samples of plasma and urine obtained at the first visit to hospital by the single radial gel diffusion technique (Adeniyi *et al.*, 1976). Plasma albumin was standardised using a previously calibrated serum standard. PCV, WBC, and platelet counts were done 6 times in the first two weeks of treatment, and then at each visit. Renal biopsies were classified as previously described (Hendrickse *et al.*, 1972).

Management. All patients entering the trial were in hospital for at least 2 weeks for diagnosis and starting treatment. They were then followed up at the outpatients department where they were seen every 2 weeks for 12 weeks, when cytotoxic treatment was stopped in most, after which they were seen less often for up to 5 years.

All patients were initially treated for malaria with a combination of chloroquine and primaquine, and received a high protein, low sodium diet, and the diuretic hydroflumethiazide. At each outpatient attendance drugs to last until the next visit were dispensed and any unused tablets were brought back to check on correct drug dosage at home. Patients were instructed to return immediately in the event of any untoward reactions or intercurrent illness. Full clinical examination, including blood pressure, was done at each visit and any illness was promptly treated, with hospital admission if necessary.

Results

There was no significant difference in ages, plasma albumin levels, CG/CA, or renal biopsies in the three groups. *P. malariae* were seen in blood films from 27 of the 36 patients. Blood urea and serum electrolytes were within normal ranges and only one patient had a blood pressure > 120/80mmHg at the first visit. 31 patients had renal biopsies; in all the lesions were characteristic of quartan malaria nephropathy. Immunofluorescence examination was positive for IgG in all 27 studied, and in all but one for C3.

Two patients treated with cyclophosphamide and 2 treated with azathioprine had complete clinical remissions with loss of proteinuria (trace or 0) by the 8th week of treatment, but none in the control group. Of these the 3 in whom biopsy was done showed mild QMN lesions, positive for IgG and C3. All patients showed a rise in serum albumin which was probably due to better feeding. Six other patients treated with cyclophosphamide improved considerably, as shown by loss of oedema, rise in serum albumin to normal levels, and reduction in proteinuria (Albustix + on 3 consecutive urine testings), which reflects a substantial reduction of albumin clearance (Table 1). The other children had no reduction of proteinuria detectable by these tests (Albustix 3+ 4+) and serum albumin remained well below 20 g/l. More patients in the cyclophosphamide-treated group improved than did those in either the control or the azathioprine group.

The cytotoxic drugs had a number of adverse effects. Some patients complained of anorexia, nausea, and vomiting when either drug was given in the morning, but this was overcome by giving it at night. It was necessary to withdraw cyclophosphamide in 2 patients, in one because of severe haemorrhagic cystitis and in the other (subsequently shown to have severe renal amyloidosis) because of rapid deterioration, severe skin infection, bronchopneumonia, and septicaemia. Both drug-treated groups had significantly more infections than the control group. The main infections were of the skin and bronchopneumonia (Table 2). The organisms most often isolated from skin lesions were *Staphylococcus aureus*. The patients responded to treatment with antibiotics to which organisms were sensitive.

Table 1 *Treatment groups and outcome in the 36 patients*

	Control (*n = 12*)	*Azathioprine* (*n = 12*)	*Cyclophosphamide* (*n = 12*)
Remission	0	2	2
Improvement	0	2	8†
Deaths			
2 years	3	8*	2
4 years	5	9	6
5 years	5	9	6

*Significantly higher than control group (P = 0·05) and cyclophosphamide-treated group (P = 0·018).

†Significantly higher than control group (P = 0·001) and azathioprine-treated group (P = 0·018).

Table 2 *Number of patients with major infection during treatment (with significance of difference from control group)*

	Control (*n = 12*)	*Azathioprine* (*n = 12*)	*Cyclophosphamide* (*n = 12*)
Bronchopneumonia	2	8 (P = 0·018)	6 NS
Staphylococcal skin infection	1	6 (P = 0·034)	7 (P = 0·014)

No patient died during the drug treatment period and in none did PCV, WBC, or platelet counts fall below normal limits.

Regular outpatient follow-up was planned for 5 years after the treatment. Some patients did not attend, and attempts were made to get into contact with them at home. The 5 patients who did not attend and were not traced, and who had had hypertension and raised levels of blood urea on the last visit, have been classified as presumed dead; one with normal blood pressure and blood urea after full remission at 4 years was presumed alive at 5 years. The 4 patients who had complete remissions remained well throughout follow-up. The mortality in the 5 years of follow-up is shown in the Figure. Only one child died in the first year (of renal failure due to renal amyloidosis). There were significantly more deaths in the azathioprine-treated group than in the other two, in the 2nd year of the follow-up (Table 1). There was no obvious relationship between time of death and the initial renal biopsy histology or differential protein clearance. In most children who died, death was preceded by hypertension and raised levels of blood urea and the deaths were regarded as being due to renal failure. At necropsy contracted kidneys were found in all.

The 4 patients who showed rapid disappearance of proteinuria remained well and free of proteinuria throughout the period of follow-up. The diminished proteinuria initially observed in the cyclophosphamide-treated group appears to have had no influence on prognosis as, after 2 years, mortality rose and was similar to that in the control group but was still lower than in the azathioprine-treated group.

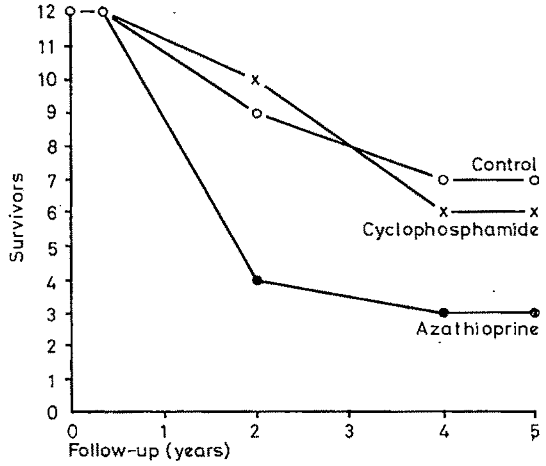

Figure *Number of nephrotic children in each group surviving at each follow-up period. The allocation of nonattenders is explained in the text.*

Since completing the trial cyclophosphamide has been used in 13 more such patients, and the same procedure was used. Three lost their proteinuria and 4 showed considerable reduction. Three other patients with nephrotic syndrome were given cyclophosphamide in gradually increasing doses until neutropenia (WBC $<3000/\text{mm}^3$; $<3\cdot0\times10^9$/l) resulted when the drug was discontinued. No therapeutic benefit was noted. In 9 other patients treated with azathioprine no benefit of treatment was noted.

Discussion

The findings in this study confirm previous reports of the gravity of the prognosis in nephrotic syndrome in Nigerian children and the generally poor response to immunosuppressive treatment. Kibukamusoke (1968) reported an impression of benefit from treatment with azathioprine, not found in this or in previous studies undertaken in Ibadan (Adeniyi *et al.*, 1970). Our findings show that azathioprine does not generally control proteinuria, and that its use is associated with a much higher risk of infection and a significant reduction in the 2-year survival rate. On the available evidence, azathioprine must be regarded as contraindicated in the treatment of nephrotic syndrome in West African children.

The increased mortality due to renal failure observed in patients treated with azathioprine is interesting and could be an example of the postulated system in which a drug may accelerate renal disease by causing more damage to mechanisms concerned with antigen clearance than to the mechanism causing the renal damage (Soothill and Steward, 1971; Steward *et al.*, 1973). Some of the changes observed in immunofluorescence findings on renal biopsies in some azathioprine-treated cases of nephrotic syndrome (Houba *et al.*, 1970) could be interpreted as having arisen from such an effect.

Cyclophosphamide treatment was associated with remission in 2 patients and a significant reduction of proteinuria in the group as a whole, but this was not associated with improved survival; there were serious side effects during treatment, especially infections. The absence of full remission in the control group and our previous experience, suggest that the occasional complete remission may be an effect of cyclophosphamide, and that response is more likely in those with a relatively short history (< 3 months), and relatively mild histological lesions (QMN grade I, Hendrickse *et al.*, 1972). It seems sensible, therefore, to limit the use of this drug to patients who satisfy these criteria, and who can be closely supervised during treatment. Selectivity of proteinuria, useful for predicting corticosteroid response in

Nigerian nephrotic children (Adeniyi *et al.*, 1976) does not predict recovery after cyclophosphamide in those with relatively poorly selective proteinuria.

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Serum gastrin levels in hypertrophic pyloric stenosis of infancy

Response to a gastrin secretion test

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SUMMARY The aim of this study was to look for a difference in fasting serum gastrin levels or in serum gastrin response to oral feeding between infants with hypertrophic pyloric stenosis and normal controls. Fasting serum gastrin levels were measured by radioimmunoassay in 10 patients with pyloric stenosis, before pyloromyotomy and 7 and 15 days after it, and in 11 controls. In addition, the serum gastrin responses to a casein hydrolysate meal were studied in both groups (in the patients, 7 days after operation). The fasting serum gastrin levels in the patients did not differ from those in the controls before operation, but they did so after it. The serum gastrin response to feeding in patients after pyloromyotomy was no greater than in controls.

Since the introduction of sensitive methods for measuring gastrin (McGuigan, 1968; Yalow and Berson, 1970), this hormone has been studied in normal children (Sann *et al.*, 1975; Niessen *et al.*, 1976) and it is suggested that serum levels vary with age. The mechanisms responsible for the secretion of gastrin are present at birth. Serum gastrin level is higher in the blood of neonates than in peripheral maternal blood (von Berger *et al.*, 1976; Euler *et al.*, 1977), and rises after the first feed, continuing to rise steeply for a few days after birth (Rogers *et al.*, 1974). The hypothesis that increased gastrin secretion may induce hypertrophic pyloric stenosis in infancy receives support from experimental studies. Pyloric stenosis has been observed in newborn pups after repeated injections of pentagastrin to pregnant bitches during the final stages of gestation, and the most pronounced changes were seen in 30-day-old pups that continued to receive pentagastrin after birth (Dodge, 1970; Karim *et al.*, 1974; Dodge and Karim, 1976). Moreover a direct action of gastrin on the pyloric circular muscle has been demonstrated (Rogers *et al.*, 1976), in addition to an increase of antral mobility induced by the hormone *in vitro* (Bennett, 1965) and *in vivo* (Heinische, 1967; Isenberg and Grossman, 1969). Gastrin released by vagal reflexes may act in newborn babies as a mediator of perinatal environmental stress factors (Dodge, 1975) to produce pyloric contraction or spasm, or both, and pyloric hypertrophy; alternatively the pyloric hold-up could be increased by a self-perpetuating mechanism: antral distension with milk and gastrin release (Dodge, 1972; Rogers *et al.*, 1975).

The presence of hypergastrinaemia in hypertrophic pyloric stenosis has been denied by some investigators (Rogers *et al.*, 1975) and supported by others (Spitz and Zail, 1976). The aim of this study was to determine fasting serum gastrin levels in infants with hypertrophic pyloric stenosis before and after pyloromyotomy. In addition, the serum gastrin response to oral feeding was determined so as to find out whether the response is exaggerated in infants with hypertrophic pyloric stenosis.

A rise in serum gastrin after feeding different milks to normal newborn babies and infants has been shown (Sann *et al.*, 1975; von Berger *et al.*, 1976). It was found that high or pure protein preparations are capable of producing a gastrin release with a

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substantial rise in serum gastrin (Konturek *et al.*, 1974). Hydrolysed proteins, and especially free amino-acids, are potent gastrin stimulants (Elwin, 1974; Walsh *et al.*, 1975). There have been no systematic surveys of amino-acids to determine which one releases gastrin. In man, glycine alone has been tested and shown to be a weak stimulant (McGuigan and Trudeau, 1970). The most active releasers of gastrin (serine, valine, and tryptophan) are amino-acids that are rather poor stimulators of acid secretion (Konturek *et al.*, 1977).

Material

After informed parental consent had been obtained the following groups of patients and controls were studied.

Patients. 10 (9 boys and one girl, age range 3 weeks–4 months) infants with hypertrophic pyloric stenosis without radiologically demonstrable gastro-oesophageal reflux.

Controls. 11 (6 boys and 5 girls, age range 3 weeks–4 months) infants with no gastrointestinal or neurological disease.

Development in both groups of babies was normal. All infants were between 3rd and 97th centiles for length as there is evidence relating gastrin levels to body size.

Methods

All blood samples were drawn via an indwelling catheter already in place or by direct venepuncture at the time an indwelling catheter was placed as part of the patient's treatment. 2·5 ml blood was collected in an unheparinised test-tube, with the separated serum stored at −20°C. Serum gastrin was measured by radioimmunoassay (Yalow and Berson, 1970). The specific antisera used were raised by immunisation with repeated injections of synthetic human gastrin 1 (G1 S(1–17)) conjugated to ov-albumin in rabbits. The G1 S1-17 was labelled with iodine-125 (Inserm U 10, Paris) and standard gastrin was obtained from Imperial Chemical Industries Ltd. Separation of bound antibody from free hormone was by dextran-coated charcoal.

Gastrin secretion test. This was performed by administering casein hydrolysate (Amirige, Nutricia, Netherlands) containing 85·5% nitrogenous substances of which 87·5% are polypeptides (di-, tetra-, and hexapeptides) and 12·5% are free amino-acids. The composition per 100 g Amirige was: polypeptides 74·86; free amino-acids 10·84. Essential amino-acids: leucine 1·67; lysine 1·51, methionine 1·33, phenylalanine 1·33, isoleucine 0·15, histidine 0·07, threonine 0·07. Non-essential amino-acids: arginine 1·85, tyrosine 1·71, aspartic acid 0·50, glutamic acid 0·45, serine 0·17.

The compound was prepared in such a way as to contain identical protein concentrations for each infant in the same amounts that he would have received with normal feeding (150 ml of half-cream cows' milk/kg per day containing 132 ml H_2O, 4·20 g protein, and with a caloric value of 103, and given in 6 feeds of 25 ml/kg). The amount of the preparation given at each feed was thus 0·70 g peptides/kg (1 g Amirige = 0·855 g peptides). A 15-min gastric drip feed was used to administer these amounts to each infant after a 6-hour fast. The results in the two groups were recorded and plotted on a curve showing changes in serum gastrin levels at −15, 0, 5, 10, 15, 30, and 60 min from the beginning of the feed. In the patients, gastrin stimulation was carried out on the 7th postoperative day when normal oral nutrition had been resumed. Fasting serum gastrin levels were also determined in these patients before pyloromyotomy and 2 weeks later. The preoperative samples for fasting serum gastrin determination were obtained at least 4 hours after the last feed and the postoperative samples, as in the control group, after a 6-hour fast. Statistical comparison of groups was by Student's *t* test.

Results

Fasting serum gastrin levels. In the control group the mean fasting serum gastrin level (± SEM) was 134·2 ± 18·2 pg/ml. The mean fasting level in the patients before pyloromyotomy did not differ from those in the control group, but these levels did differ ($P<0·025$) after operation. In the patients the mean fasting levels before operation and on the 7th and 15th postoperative days were, respectively, 129·5 ± 23·2, 222·2 ± 39·6, and 197·5 ± 21·7 pg/ml. The differences between the preoperative values and those on the 7th and 15th postoperative days were significant ($P<0·05$ and $P<0·025$ respectively) (Table 1).

Serum gastrin response to feeding. In the control group a substantial rise was noted within the first minutes after the feed with a maximum peak at 10 min, immediately followed by a decline, which was steep to 15 min, becoming more gradual thereafter to 30 min. Basal gastrin levels were regained after 60 min (Fig. 1). The mean basal and peak serum gastrin levels (± SEM) were respectively 134·2 ± 18·2 and 247·5 ± 26·4 pg/ml;

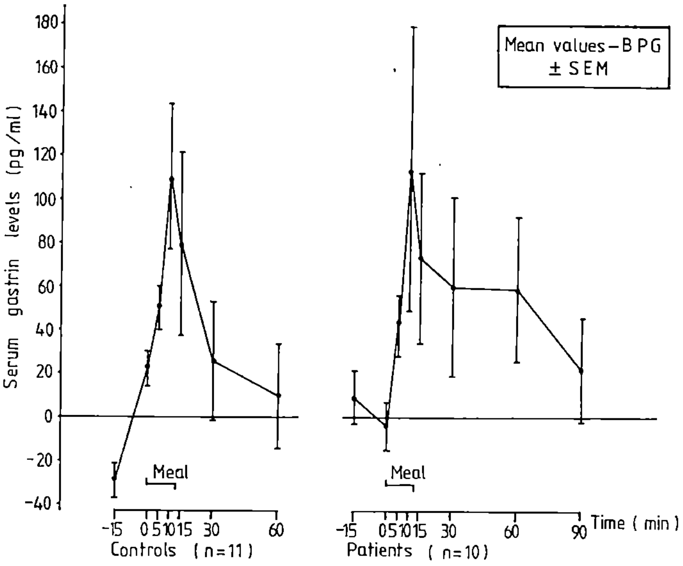

Fig. 1 *Mean serum gastrin levels (pg/ml ± SEM) in 11 control infants and 10 patients with hypertrophic pyloric stenosis after a casein hydrolysate meal. The results are expressed as the mean of all values obtained at each time, less the mean basal serum gastrin levels (BSG) (this explains initial negative values).*

Table 1 *Fasting serum gastrin levels (pg/ml) in 10 patients with hypertrophic pyloric stenosis before and after pyloromyotomy*

Case	*Before operation*	*After operation*	
		7 days	*15 days*
1	260	290	260
2	155	135	295
3	125	113	140
4	215	175	250
5	47	365	135
6	61	415	230
7	190	375	265
8	52	140	160
9	98	89	120
10	92	125	120
Mean±SEM	129·5 ± 23·2	222·2 ± 39·6	197·5 ± 21·7

these values differed significantly (P < 0·02) (Fig. 2).

In the patients the serum gastrin response to stimulation was represented by a curve with a levelling-off effect between 30 and 60 min, and a more slowly decreasing slope to baseline value beyond 90 min (Fig. 1). The mean basal and peak serum gastrin levels were 222·2 ± 39·6 and 359·5 ± 56·5 pg/ml, and differed significantly (P<0·02) (Fig. 2).

The peak levels obtained after maximum gastrin stimulation were higher in the patients than in the controls (P < 0·05), but when the increased values were compared as the percentage of basal gastrin levels ((PSG − BSG)/BSG) there was no significant difference (P<0·1) (Table 2). Analysis of the decreasing slope by comparing the mean gastrin

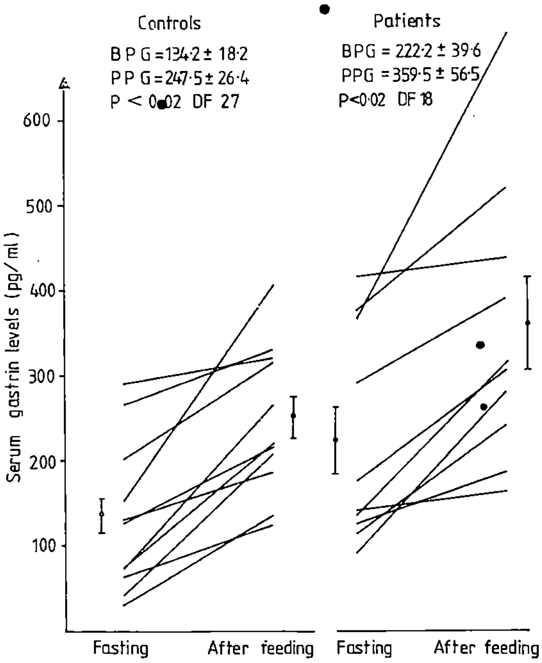

Fig. 2 *Mean basal serum gastrin (BSG) levels and peak serum gastrin (PSG) levels (pg/ml ± SEM) in 11 control infants and 10 patients with hypertrophic pyloric stenosis after a casein hydrolysate meal. The serum gastrin response to the meal is shown by comparing BSG (for each infant, mean value of 2 fasting levels at −15 and 0 minutes) and PSG (for each infant, mean value of the 2 highest levels obtained).*

Table 2 *Mean peak serum gastrin levels (pg/ml ± SEM) in response to a casein hydrolysate meal in 11 control infants and in 10 patients with hypertrophic pyloric stenosis 7 days after pyloromyotomy. Significance of PSG and of percentage of basal gastrin levels*

Value	*Control infants* (*n = 11*)	*Patients* (*n = 10*)
PSG	247·5 ± 26·4*	359·5 ± 56·5
(PSG–BSG)/BSG	1·56 ± 0·42†	0·78 ± 0·20

PSG = peak serum gastrin level, BSG = basal serum gastrin level.
*Significant ($P<0{\cdot}05$) DF 19, †not significant ($P<0{\cdot}10$) DF 19.

levels at 30 and 60 min in both groups showed that there was no difference despite the levelling-off effect seen in the patients (at 30 min, $P<0{\cdot}25$; at 60 min, $P<0{\cdot}15$) (Fig. 1).

In patients, increased fasting gastrin levels were present after pyloromyotomy and were still present 2 weeks after the operation. Test meals did not produce an exaggerated gastrin response and the results were of the same order as those obtained by the same trial stimulation in controls.

Discussion

These findings cast doubt on the hypothesis that increased gastrin levels may promote and/or maintain hypertrophic pyloric stenosis of infancy. This doubt is reinforced by the fact that little difference in serum gastrin levels between the healthy and the affected children was found in the preoperative phase.

Nevertheless higher levels were found in the postoperative period. A marked rise in mean fasting levels was also noted 4 and 5 days after operation by Rogers *et al.* (1975) and Spitz and Zail (1976). Such a hypergastrinaemia does not appear to be induced solely by antral distension secondary to pyloric obstruction, as it was still present in our patients 7 to 15 days after pyloromyotomy. This interpretation can be questioned because, although pyloromyotomy relieves clinical obstruction and motility returns within 30 hours (Schärli and Leditschke, 1968), radiological evidence of improvement of the pylorus does not appear until after some weeks or months (Bishop and Hope, 1962). The possibility that distension of the antrum can persist during the postoperative period is therefore not eliminated.

The postoperative hypergastrinaemia could be explained by an inverse relationship between the serum gastrin levels and HCl secretion. Dodge (1976) found that in preoperative children with pyloric stenosis, acid secretion was raised, probably by increased parietal cell mass. This increased acid secretion may decrease basal gastrin secretion by lowering the intraluminal pH. After operation, basal gastric acid secretion falls and it seems that gastrin secretion increases. In our series the fasting gastrin levels showed a significant increase after operation in only 5 out of 10 patients, 3 of whom had the lowest preoperative levels (Cases 5, 6, and 8) (Table 1). Perhaps these low levels indicate that their acid secretion was increased to the point where gastrin release was being inhibited. The reduced gastric acidity found after 7 days would allow these patients to revert to a fasting serum gastrin level more in keeping with their true gastrin secretion level. In any event, these 5 patients responded normally to feeding when tested postoperatively. For obvious reasons the gastrin secretory capacity was not tested in preoperative patients.

Long-term follow-up of patients with pyloric stenosis by Wanscher and Jensen (1971) showed an increased incidence of ulcer symptoms, and many had an increased basal gastric acidity. This might indicate that the hypergastrinaemia persists indefinitely and raises another question, whether hypergastrinaemia is the only long-term result of hypertrophic pyloric stenosis.

Although it was confirmed that gastrin levels after feeding were greater in the patients than in the controls, we would emphasise that the differences are insignificant when they are related to the basal gastrin levels. Thus, our findings do not support the hypothesis that patients with pyloric stenosis may have an exaggerated gastrin response to feeding after pyloromyotomy.

Addendum

Since this paper was written, Janik *et al.* (1977) have confirmed that the wide range of serum gastrin levels in normal infants and children is dependent on age, body surface area, and duration of fast. Rogers *et al.* (1978) failed to demonstrate a significant rise in serum gastrin levels after normal newborn infants ingest protein-containing milk. Werlin *et al.* (1978) measured serum gastrin levels in cord blood of infants in whom pyloric stenosis subsequently developed and in controls, and found little difference.

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Transpyloric feeding in the very low birthweight (1500 g and below) infant

One year's experience in an intensive care neonatal unit

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SUMMARY The success of transpyloric feeding in a group of babies weighing 1500 g or less was evaluated. This method was successful for most well babies but for many of those who required respiratory assistance (usually by face mask) it was not.

Although babies weighing <1500 g at birth represent only 1% of the total live births in the United Kingdom, they now present the biggest management problem in intensive care baby units. The importance of early feeding and the provision of adequate calories in the first weeks of life has been emphasised (Smallpeice and Davies, 1964; Winick, 1969; Lubchenco *et al.*, 1972). Milk feeding via nasogastric tube is not always satisfactory in the very low birthweight infant, mainly because of the dangers of regurgitation and aspiration. The introduction of jejunal feeding (Rhea and Kilby, 1970; Cheek and Staub, 1973), and the greater use of IV feeding (Shaw, 1973) have, to some extent, made it easier to provide an adequate calorie intake for very small babies. Although there is no controlled evidence, greater experience with total parenteral nutrition may be one of the important factors associated with a higher survival rate of the most immature. Nevertheless milk feeding is likely to have greater application in units with limited laboratory and staff resources as it does not require such frequent monitoring. We report our experience from a neonatal referral unit during a 12-month period when milk feeding was electively practised whenever possible, in the hope that it may help others. This paper presents details of methods of feeding in 69 babies weighing <1500 g at birth who were admitted to the Hammersmith Hospital between 1 January and 31 December 1977.

Patients and methods

During 1977, 95 babies of birthweight 1500 g or less were admitted to the intensive care baby unit. 28 (29%) were born in the hospital, the others were admitted from other units in and near London. The overall survival rate was 53%. In Table 1, the 95 babies are grouped according to birthweights (<1000 g, and 1000–1500 g) and gestational ages (28 weeks or less, 29–30 weeks, 31–32 weeks, and >32 weeks). The number who needed respiratory assistance (RA) (either intermittent positive pressure ventilation (IPPV) or continuous inflating pressure (CIP)) in each subgroup is also shown.

Feeding data on 69 of the 95 babies are presented. The remaining 26 are excluded for the following reasons: 22 died within 4 days of admission (all were ventilated from the time of admission); 3 were admitted when >2 weeks old; one had congenital heart disease and was admitted for a short period only.

The policy in the unit during the period of the study was to feed all babies if possible with milk, expressed breast milk if available otherwise low

Table 1 *Survival rates of all babies weighing 1500 g or less at birth admitted to the unit during 1977*

	Babies		*Respiratory assistance*	*No assistance*	*Survivors**
	No.	(%)			
Birthweight (g)					
<1000	32	(34)	28	4	7
1000–1500	63	(66)	32	31	43
Gestational age					
28 weeks and less	43	(45)	37	6	9
29–30 weeks	26	(27)	16	10	17
31–32 weeks	18	(19)	5	13	16
>32 weeks	8	(8)	2	6	8
Totals	95		60 (63%)	35 (37%)	50 (53%)

*Survival rate for those born at this hospital = 64·3%, for those born outside = 47·8%.

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solute cows' milk. Apart from 3 babies who were fed entirely intravenously, IV feeding was used only when milk feeds could not be established. Jejunal feeding was attempted in all but the healthiest of babies.

Method of passage of jejunal tubes. The jejunal tubes were made of silicone, weighted with an end-hole stainless steel tip. The outside diameter was 1·7 mm and the inside diameter 0·8 mm. The glabella-to-heel distance was measured and the length marked on the tube with a piece of black cotton. During the first 3 months of the study period, all tubes were passed via the nose. Later an increase in nasal resistance was found in babies with nasal tubes in place (J. Stocks, 1977, unpublished), so the tubes were subsequently passed through the mouth. The tube was passed into the stomach, without an introducer, and the baby was then turned on to his right side; the tube was advanced at intervals varying between 20 min and one hour, depending on how well the baby tolerated the procedure. The position of the tube was checked by introducing 2 ml sterile water down the tube and then aspirating via an orogastric polyvinyl feeding tube. If no water was aspirated the tube was assumed to have passed through the pylorus. (It was not possible to suck back directly via the silastic jejunal tube because suction resulted in the lumen collapsing.) If any doubt remained the position of the tube was checked by *x*-ray.

After feeding had begun the stomach was aspirated every 2–4 hours to ensure that it was free of milk—i.e. the tube had not slipped back.

Attempts were made to pass the tubes as soon as the babies were settled in the unit. IV fluids (5% dextrose in the first 48 hours and dextrose/saline thereafter) complemented the milk intake initially to meet the full daily fluid requirement: 60 ml/kg day 1, 90 ml/kg day 2, 120 ml/kg day 3, 150 ml/kg day 4, increasing to 200 ml/kg at the end of the first week. A supplement of 30 ml/day of water was given to all babies on an open incubator and to those who received phototherapy. No tubes were passed if babies required assisted respiration by face mask, but attempts were made to continue feeding if the tube was known to be in place when the face mask was applied.

Results

Three babies received IV feeding only. The other 66 babies are divided into 3 main groups: group 1, babies fed via gastric tube; group 2, babies fed via nasal jejunal tube; group 3, babies fed via oral jejunal tube. Groups 2 and 3 are subdivided into: (a) those babies requiring no respiratory assistance other than an increase in inspired oxygen; (b) those requiring either IPPV or CIP at some time in the neonatal period.

12 babies were fed via gastric tubes. All but 3 of these were of at least 32 weeks' gestation (mean birthweight 1225 g, mean gestational age 32·4 weeks) and were considered by nursing staff to be well enough to tolerate gastric feeding.

19 babies had jejunal tubes passed via the nose, 35 via the mouth. The mean birthweights of these two groups were 1067 and 1171 g, mean gestational ages 29 and 30 weeks, and the number requiring respiratory assistance was 53 and 57% respectively.

In each case, the time when the feeding tube was first passed, the time taken for it to reach the jejunum, the volumes of milk given, the complications, and the reasons for stopping jejunal feeding were recorded.

Table 2 shows the day on which passage of a feeding tube was first attempted.

The time taken for the jejunal tubes to be satisfactorily positioned is shown in Table 3. Three babies (all <1000 g) in whom jejunal tubes could not be introduced orally because of repeated regurgitation, subsequently had them passed successfully through the nose.

32 babies were fed for at least 3 days and 11 were fed for at least a week. The longest period was 39 days. In 7 babies the jejunal tube was not satisfactorily placed and 6 babies had tubes in place but

Table 2 *Day on which feeding tubes were passed (from day of admission to unit)*

Group	*No. in group*	*Day*			
		1	*2*	*3*	*>4*
1	12	6	0	3	3*
2a	9	7	2		
2b	10	7	2	1*	
3a	15	7	3	4	1
3b	20	9	3	3	5*
Total	66	36 (55%)	10 (15%)	11 (17%)	9 (14%)

*Fed after period of respiratory assistance.

Table 3 *Time taken for jejunal tubes to be satisfactorily positioned*

Group	*No. in group*	*<24 hours*	*24–48 hours*	*48–72 hours*	*Not in place*
2a	9	7	1	1	
2b	10	6	2		2
3a	15	7	5		3*
3b	20	10	3	2	5
Total	54	30 (56%)	11 (20%)	3 (6%)	10 (19%)

*All 3 babies had nasal jejunal tubes successfully passed eventually and in subsequent results are included in group 2a.

were not fed. The reasons for stopping, or not starting jejunal feeds, are shown in Table 4.

In addition to the 5 babies who developed necrotising enterocolitis during jejunal feeding, 3 other babies developed the condition, one while a jejunal tube was being positioned and one after jejunal feeds had been stopped because of apnoea. The time of onset in the third case was not known, the diagnosis being made at necropsy.

Table 4 *Reasons for stopping or not starting jejunal feeds*

Group	*No.*	*Reason*	*Outcome*
2a	12 (3 previously attempted through the mouth)	Electively stopped Pulled out by baby NEC Tube in place but not fed (1 abdominal distension, 2 apnoea)	5 3 1 3
2b	10 (7 passed before RA)	Not in place Bile-stained aspirate Aspiration before IPPV Aspiration during CIP Apnoea Oral feeds continued until death	2 1 1 1 1 1
	1 passed during RA	Bile-stained aspirate	1
	2 passed after RA	Electively stopped	2
3a	15	Not in place (transferred to 2a) Electively stopped Pulled out by baby NEC Out of position after initial satisfactory placement Tube in place but not fed (apnoea)	3 3 4 2 2 1
3b	20 (9 passed before RA)	Not in place Apnoea Aspiration during RA NEC	1 5 1 2
	7 passed during RA	Not in place Pulled out by baby In place but not fed (poor condition of baby) Feed continued until death)	4 1 1 1
	4 passed after RA	Electively stopped Pulled out by baby Out of position after initial satisfactory placement	1 2 1

NEC = necrotising enterocolitis, RA = respiratory assistance (IPPV or CIP).

Intravenous feeding. 22 babies required IV feeding at some time during the neonatal period because of failure to establish milk feeds (6), recurrent apnoea (5), respiratory assistance from birth (6), and necrotising enterocolitis (5). Attempts had already been made in most of these babies to pass jejunal tubes.

In Table 5, a comparison of the mean maximum weight loss, the mean time to regain birthweight, and the mean volume of milk given to the survivors (45 of the 66 babies studied) in the three groups is shown.

Discussion

Until 1975, in this unit, all babies weighing <1500 g at birth, and receiving milk, were fed intragastrically via polyvinyl tubes introduced through the nose. Because of the increasing numbers of small, immature babies, and the impressive success of Rhea and Kilby (1970) with the feeding of babies transpylorically, it was decided to adopt jejunal feeding in preference to IV feeding as we believed that there would be fewer complications.

Because of the association of polyvinyl feeding tubes with perforation (Boros and Reynolds, 1974; Chen and Wong, 1974; Loo *et al.*, 1974), we chose silastic tubing as recommended by Rhea and Kilby (1970). However perforation with a silastic transpyloric tube has recently been described (Pérez-Rodrigues *et al.*, 1978). The silicone paediatric duodenal tubes available on the market are twice the length of our tubes and we felt that this excessive dead space was undesirable, although they are much stiffer and may be easier to pass into the stomach and through the pylorus.

Many babies of birthweights 1500 g or less, will tolerate gastric feeds, and, although this choice of method was purely empirical, the babies fed by gastric tube in this study were healthy, and most were >32 weeks' gestation. We feel it advisable to nurse these babies prone to decrease the risk of aspiration.

Table 5 *Comparison of mean maximum weight loss, mean time to regain birthweight, and the mean volume of milk (ml/kg per day) received on days 1, 2, 3, 4, 7, and 14 between the survivors of groups 1, 2, and 3*

Group	*No.*		*Birthweight (g)*		*Mean maximum weight loss (g)*	*Birthweight regain (day)*	*Vol. milk feed (ml/kg per day)*					
	AGA	*SGA*	*Mean*	*Range*			*1*	*2*	*3*	*4*	*7*	*14*
1	7	4	1372	(1080–1500)	78 (5·7%)	9	36	58	89	138	167	211
2	9	3	1139	(780–1380)	113 (9·9%)	16	30	73	90	107	149	184
3	18	4	1227	(760–1500)	146 (11·9%)	17	11	35	59	76	108	150
	Total 45											

AGA = appropriate for gestational age, SGA = small for gestational age.

The results suggest that we were able to position the jejunal tubes more quickly and satisfactorily when they were passed through the nose, although the figures do not reach statistical significance. Silastic tubes are very compliant and when the oral route was used, the tubes tended to loop out of the mouth and were more liable to be pulled back during suction. Because of the increased nasal resistance (J. Stocks, 1977, unpublished) when tubes are passed through the nose, it was felt that oral tubes were preferable, particularly in the first days of life when very preterm babies are more likely to suffer respiratory disorders. The delay in correct positioning of the tubes by the oral route may explain why babies in group 3 received less milk during the first 14 days than those in group 2.

Overall, 81·5% of jejunal tubes were *in situ* within 72 hours; these figures compare with those of Cheek and Staub (1973) in which 61% of 36 infants were being fed by jejunal tubes within that time, and those of Wells and Zachman (1975) who reported 100% of 18 infants having jejunal tubes in place in less than 48 hours. Rhea *et al.* (1975) found little difficulty in introducing weighted tubes in a large number of infants of varying weights and gestational ages. Rhea and Kilby (1970) found that steel-weighted jejunal tubes were too light to pass through the pylorus and it may be that heavier, gold-weighted tubes would pass more quickly.

32 of 54 babies were fed for at least 3 days and 11 were fed for more than a week, the longest period being 39 days. Difficulties in feeding by jejunal tube were encountered, particularly in the group requiring IPPV or CIP. In most of these, this was administered by the face mask. Nasopharyngeal suction, not only in this group but also in those babies with recurrent apnoea, appeared to play a part in tubes becoming dislodged and this may have accounted for aspiration in 3 babies. Although attention should be paid to the volume of gastric aspirate in all babies, those who require nasopharyngeal suction are particularly at risk of aspirating gastric contents.

During the period of this study 8 babies developed necrotising enterocolitis, 5 while being fed by jejunal tube, one during the time that a jejunal tube was being advanced, one a few days after jejunal feeding had been stopped; in the last case, the diagnosis was made at necropsy. The part played by jejunal feeding in a condition of probable multiple aetiology is difficult to assess although alteration of bacterial flora in the jejunum with jejunal tubes (Challacombe, 1974) or local irritation may predispose to the condition.

We suggest that jejunal feeding is best used for as short a period as possible because not only is this method of feeding unphysiological but it also has recognised complications. In addition, continuous infusion of milk directly into the jejunum may alter the intestinal bacterial flora. Oral feeding with umbilical arterial catheters in place may also predispose to necrotising enterocolitis (Lehmiller and Kanto, 1978).

Babies with birthweights of 1500 g and less admitted to this unit between 1965–70 were fed by gastric tubes only (Davies and Davis, 1970; Davies and Tizard, 1975) and it is interesting to note that although those babies received a greater volume of milk/kg per day in the first 14 days of life compared with ours, the percentage weight loss and time to regain birthweight were similar. However, the much better survival rate in 1977, in addition to the use of IV feeding, and a number of other factors, all make direct comparison difficult.

This study shows that naso- or orojejunal feeding can be successfully carried out in well babies of birthweights <1500 g. However, this method of feeding for babies requiring respiratory assistance almost entirely by face mask was not successful, and such babies may benefit from a period of IV feeding until respiratory assistance is no longer required. Only 2 out of 24 babies were successfully fed while receiving respiratory assistance. Our principal complication was aspiration (3/54) but it is impossible to know if this would have been more or less with gastric feeds. It should be emphasised that intravenously feeding very low birthweight babies is not without difficulties and is best carried out in the specialised units experienced in the procedure.

We should like to thank Dr Pamela Davies for her advice in the preparation of this paper and the nursing staff of the premature baby unit for their co-operation during the study.

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Lysozyme in the tears of newborn babies

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SUMMARY Tear lysozyme concentration was measured in term, preterm, and small-for-dates infants using a modification of the lysoplate technique. The lysozyme concentration was greater in the term infant than in preterm and small-for-dates infants. The values were found to increase with birthweight and gestation to a term value which is similar to that described in adults. There was no relationship between the lysozyme concentration and the rate of tear production.

In 1922 Fleming discovered 'a remarkable bacteriolytic element' in nasal mucus which was capable of lysing certain bacteria, particularly *Micrococcus lysodeikticus*, which he called lysozyme. The lysozyme is identical in all human secretions and tissues but lysozyme in hen egg white is different (Jollés and Jollés, 1967). Lysozyme acts by breaking down cell wall mucopolysaccharides; this action has been precisely defined and this group of enzymes can be classified as muramidases or N-acetylmuramide glycanohydrolases (Chipman and Sharon, 1969). One source of human lysozyme is in the urine of patients with monocytic and myeloid leukaemia (Osserman and Lawlor, 1966). However, lysozyme is an enzyme that is found in many secretions, including human milk and human tears (Jollés and Jollés, 1967).

Sticky eyes are common in newborn infants. As a possible predisposing factor to eye infections, we wondered whether there was any deficiency in the lysozyme activity in neonatal tears. The concentration of lysozyme in adult human tears has been measured (Friedland, *et al.*, 1972; Pietsch and Pearlman, 1973; Mackie and Seal, 1976), but there has been no systematic study of the amount present in the tears of newborn babies.

Patients

Three groups of infants were studied: 20 term infants of appropriate weight for gestation, 17 preterm infants appropriate in weight for gestation, and 10 term infants who were small-for-dates (Table). Gestational age was based on the date of the mother's last menstrual period or, if this was not known, on the baby's physical and neurological characteristics (Dubowitz *et al.*, 1970). We took samples from normal uninfected eyes within the first 24 hours after birth. In most cases the baby lay quietly sleeping while samples were collected. Permission for the study was granted by the Oxford Area Health Authority (Teaching) Ethics Committee, and in each case parental permission for collecting the samples was obtained.

Table *Characteristics of the three groups of babies*

	Term (*n* = *20*)	*Preterm* (*n* = *17*)	*Term* (*small-for-dates*) (*n* = *10*)
Birthweight (kg)			
Mean	3·40	2·19	2·49
Range	2·72–4·04	1·05–3·12	2·02–2·81
Gestation (weeks)			
Mean	39·8	33·7	38·9
Range	37–41	28–36·5	37–41

Method of measuring tear lysozyme concentration

The tears were collected by the method described by Schirmer (1903). A commercially available standardised sterile strip of filter paper (Schirmer tear test: SMP International Inc.) was bent at a right-angle at the notch, 5 mm from one end. This was gently hooked over the lower lid so that the short rounded 5 mm portion was resting in the lower conjunctival sac at the medial side of the eye. After exactly 5 minutes the strip was removed and the length beyond the notch which had been wetted by tears was measured. Occasionally, if the rate of tear production was high, the strip was removed when the whole of its length (30 mm from the notch)

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became wet, and the time noted. In this way we obtained a crude index of the rate of tear production, as well as obtaining a sample of tears.

'Lysoplates' were prepared according to a modification of the method of Bonavida and Sapse (1968). 1% mass/vol. agarose was dissolved in 0·066 mol/l sodium phosphate buffer, pH 6·24, containing 1% sodium chloride, by heating in a boiling water bath until the agarose dissolved. This solution was cooled to 65°C and a thick suspension of *M. lysodeikticus* added to make the concentration of cells 0·05%. 10 ml of this mixture was placed in each plate, solidified at room temperature, and stored at 4°C.

The lysoplate technique depends on the measurement of the diameter of the zone of lysis in the *M. lysodeikticus* suspension produced by the lysozyme which is placed on the surface of the agarose and incubated at 37°C. Others have taken a 5 mm length of the Schirmer strip, but we found by weighing that this produced a piece of paper which varied greatly in size and therefore would carry a variable quantity of the solution. We therefore constructed a circular punch to produce discs of filter paper 4 mm in diameter so as to standardise the loading volume. To establish that this did, in fact, standardise the loading volume, a 4 mm disc was punched 5–10 mm from the notched end of a strip which had been wetted by dipping the notched end in water. The water-loaded disc was weighed on a balance accurate to one microgram. The disc was reweighed after it had dried and hence the amount of water taken up was obtained. In a series of 25 pilot experiments the mean weight of the disc was 0·975 mg (SD ± 0·086). These discs took up water with a mean weight of 1·298 mg (SD ± 0·233). We then found that a standard solution dried in air at room temperature resulted in no loss of lysozyme activity.

Other workers (Bonavida and Sapse, 1968; Peeters and Vantrappen, 1977) have drawn attention to the problems of the lysoplate method. The time of incubation (24 hours) and the temperature (37°C) are important as are the pH and ionic strength. It is important to use agarose and not agar because lysozyme binds to the latter but not to the former (Bonavida *et al.*, 1967). The thickness of the agarose in the plate is important as is the micrococcus concentration: it is preferable to use the same 'batch' of plates throughout. We showed that there was no variation in the zone of lysis produced by a lysozyme standard disc when plates were stored for a period of 4 weeks at 4°C.

A calibration curve was constructed from known standards of human lysozyme. All samples were measured using a single 'batch' of plates and an internal standard was included in each case.

Results

The rate of wetting of the strip in mm/min was used as an index of the rate of tear production and plotted against the zone of lysis; there was no correlation demonstrable. This indicates that an alteration in the rate of tear production does not affect lysozyme concentration.

Fig. 1 shows the distribution of the zones of lysis (corresponding to the lysozyme concentration) produced from each eye from each patient in the three groups (one sample was lost from one preterm infant). The zone of lysis is significantly greater in the term babies compared both with the preterm babies and the small-for-dates babies.

The zone of lysis against gestation is shown for appropriate weight for gestation babies in Fig. 2. The lysozyme concentration increased with increasing gestational age. The mean zone of lysis for term babies, 27·3 mm, corresponds to a lysozyme concentration of 1118 µg/ml. Fig. 3 shows the zones of

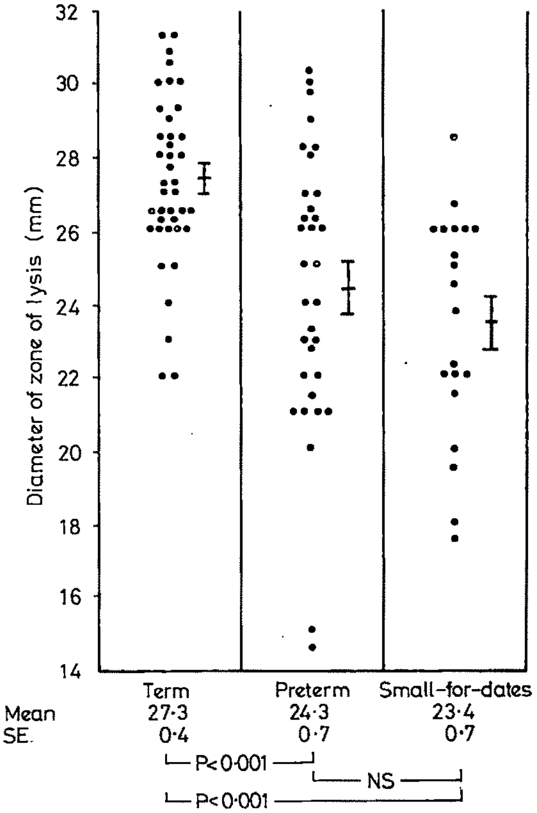

Fig. 1 *Diameters of the zone of lysis produced in the three groups of babies. Means ± 1 SE.*

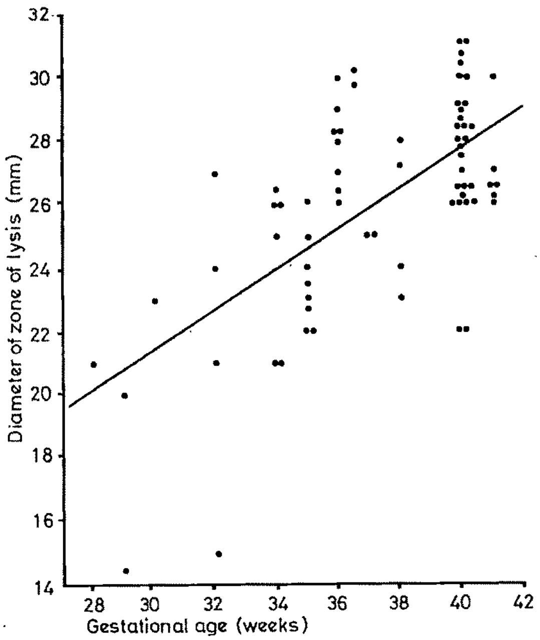

Fig. 2 *Diameter of the zone of lysis plotted against gestation in appropriate weight for gestation babies.* $r = 0 \cdot 65, P<0 \cdot 001$.

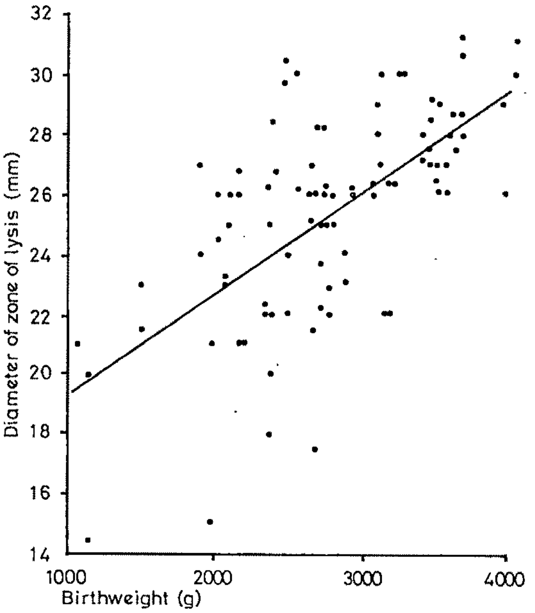

Fig. 3 *Diameter of the zone of lysis plotted against birthweight for all babies.* $r = 0 \cdot 65, P<0 \cdot 001$.

lysis plotted against birthweight for all babies, including the infants born at term small-for-dates. The lysozyme concentration increases with increasing birthweight.

Discussion

There are at least 7 tear proteins (Josephson and Weiner, 1968; Sapse *et al.*, 1969) of which the main components are pre-albumin, lysozyme, lactoferrin, and immunoglobulin A (Broekhuyse, 1974). Ridley (1928) described the bactericidal action of tear 'lysozyme' on a wide variety of micro-organisms and it later became clear that although lysozyme may be effective and protective against some pathogenic bacteria, the concentration has only to be decreased slightly for it to become ineffective (Ridley, cited by Regan, 1950). Thompson and Gallardo (1941) found that the antistaphylococcal action of tears was destroyed by acidification and heating, although the lysozyme content remained unaltered. Subsequently Friedland *et al.* (1972) demonstrated a potent 'non-lysozyme antibacterial factor' in tears.

The normal values for human tear lysozyme in adults was found by Bonavida and Sapse (1968) to be about 1700 μg/ml, although the values in their 4 infants were less (700–800 μg/ml). The mean result for our term infants was 1118 μg/ml which lies between these two values. However, the concentration of tear lysozyme varies with both gestation and birthweight.

In 1928 Ridley found a decreased lysozyme activity in certain eye diseases, including epiphora, and other workers have subsequently confirmed this (Sapse *et al.*, 1968; El-Gammal and Mostafa, 1971). One suggestion has been that an increased flow of tears produces a dilution effect. In normal eyes, however, Mackie and Seal (1976) showed very little difference in lysozyme concentration between slow and fast tear producers, and our results with neonates are similar.

It seems that newborn infants without eye infections have no marked deficiency of tear lysozyme. Preterm infants are not generally thought to be especially prone to eye infections, yet the lysozyme concentration in tears is lower with shorter gestation.

However it is likely that tear lysozyme represents only one of a wide range of synergistic antimicrobial factors. We have no additional information on these other factors in the newborn eye, nor on how the levels of lysozyme and nonlysozymal factors behave in infants with conjunctivitis.

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Lomotil poisoning in children

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SUMMARY 45 children were admitted to hospital after ingesting varying quantities of diphenoxylate (Lomotil). One died and 44 recovered without any sequelae. Four patients were comatose, 32 were drowsy, and 9 suffered respiratory depression. No correlation was found between ingested dose and the severity of symptoms. Because of its action in rendering the gut atonic, removal of diphenoxylate by gastric lavage is mandatory, even in patients admitted at least 24 hours after drug ingestion. Naloxone is the narcotic antagonist of choice, and should be used in all cases where suspected diphenoxylate poisoning leads to respiratory depression or coma. The use of Lomotil as an antidiarrhoeal agent in children is difficult to justify.

Diphenoxylate (Lomotil), widely used for the symptomatic relief of diarrhoea, was first marketed in America in 1961, each tablet or 5 ml of syrup containing diphenoxylate hydrochloride 2·5 mg and atropine sulphate 0·025 mg (Ginsburg, 1973). The atropine was added to discourage narcotic abuse by causing unpleasant effect in excessive dose. It was first marketed in the United Kingdom in 1963. Although there are few adverse reactions in adults, Lomotil may result in serious toxicity in children. Effects from the atropine are often present for about 3 hours until the narcotic-like actions of diphenoxylate hydrochloride begin to predominate. Respiratory depression is the most dangerous development and should be treated with narcotic antagonists and other supportive measures. The purpose of this paper is to present 45 cases of Lomotil poisoning in children and to describe its management.

Patients and methods

Between September 1966 and March 1978, 45 children (28 boys and 17 girls) were admitted to hospitals in Glasgow with Lomotil poisoning (Figure). Ages ranged between 10 months and 6¾ years, with a mean of 2½ years. The number of children from social classes I to V were 4, 14, 11, 8, and 8 respectively. In only 6 cases was the Lomotil prescribed for a diarrhoeal illness in the child and in 4 of these the child took an accidental overdose. In 30 (67%) cases the Lomotil had been prescribed for an adult relative, but in the other 9 children it was not known for whom the Lomotil was prescribed.

The clinical features of Lomotil poisoning in our patients are given in Table 1. These, on clinical grounds, were divided into three groups, according to whether the symptoms were mild, moderate, or severe. Those mildly affected had features of atropinism only—namely tachycardia, flushing, pyrexia, mydriasis, urinary retention, restlessness, and excitement. Those with moderate symptoms were drowsy and may also have had respiratory depression, while those classified as severely affected were unconscious. Using these criteria, 2 patients were unaffected, 7 were mildly, 32 moderately, and 4 were severely poisoned (Table 2). An average of 3 hours elapsed between ingestion of the drug and onset of symptoms. No correlation was found between the dose ingested and severity of symptoms. In fact, the mean dose of diphenoxylate and atropine was greater in the group with mild symptoms (2·9 and 0·029 mg/kg) than in those moderately affected (2·3 and 0·023 mg/kg), while in the severely poisoned group the dose of diphenoxylate and atropine ranged from 0·77 to 10 mg/kg and 0·007 to 0·10 mg/kg respectively. One patient in the last group, a 2-year-old

Table 1 *Clinical features in 45 cases of Lomotil poisoning*

Due to atropine sulphate	*No. of patients*	*Due to diphenoxylate hydrochloride*	*No. of patients*
Tachycardia	25	Drowsiness	32
Restlessness/ anxiety	22	Vomiting	20
Flushing	20	Respiratory depression	9
Urinary retention	7	Coma	4
Diminished reflexes	6	Abdominal pain/ constipation	4

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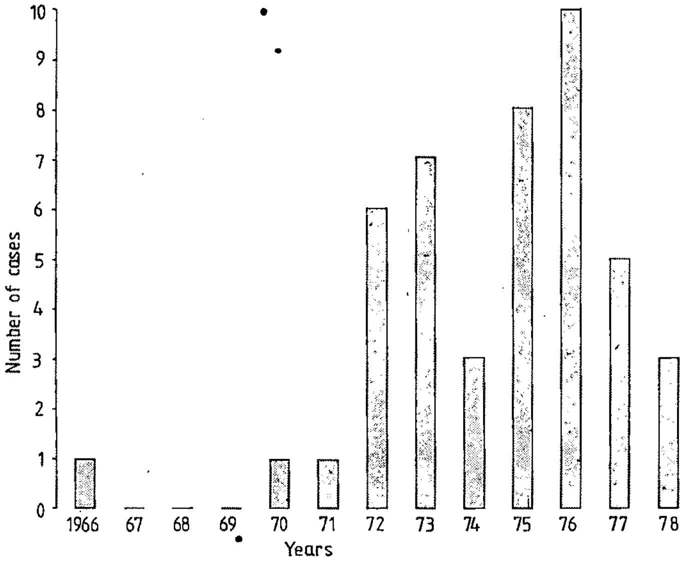

Figure *Incidence of diphenoxylate (Lomotil) poisoning from September 1966 to March 1978.*

boy, ingested possibly 27 Lomotil tablets (5·6 mg/kg diphenoxylate and 0·05 mg/kg atropine) at 7 p.m. He apparently showed no ill effects 3 hours later and so his parents put him to bed. He could not be roused the next morning at 10 a.m. and was found to be deeply comatose with laboured breathing on admission. His level of consciousness and respirations improved after 5 mg nalorphine IV but, 3 hours later without having regained consciousness, he had a respiratory arrest and was ventilated. Despite hourly injections of 0·08 mg naloxone IV he showed no subsequent response, his condition being marked by deepening coma and papilloedema. He died 48 hours after admission. Necropsy examination showed atropine in the liver 4 days after drug ingestion. Of the 9 children with respiratory depression, 2 required continuous ventilatory support. 40 patients had gastric lavage performed but, in the fatal case, this was not carried out until 26 hours after the drug was ingested. Five patients were given nalorphine (2–35 mg) and 3 naloxone (0·08 mg) as a narcotic antidote, with beneficial effects on respiratory state or level of consciousness in each case. Of those poisoned, 37 made a full recovery within 24 hours while the remaining 6 were drowsy for a longer period.

Discussion

Of the 45 patients admitted between 1966 and 1978, 29 (64%) were admitted during the last 5 years. This trend occurred despite attention being drawn to the dangers of Lomotil intoxication (*British Medical Journal*, 1973). Lomotil is an effective and safe drug for the treatment of diarrhoea in adults

Table 2 *Severity of symptoms of Lomotil toxicity*

Symptoms	*Patients (n=45)*	*Age range (years) (mean)*	*Dose ingested (mg/kg)*			*Outcome (recovered n=44)*
				Range	*Mean*	
None	2	6¾*	Diphenoxylate Hydrochloride		2·04*	Recovered
			Atropine sulphate		0·02*	
Mild	7	1 10/12–3 1/12 (2 3/12)	Diphenoxylate Hydrochloride	0·62–5·8	2·9	Recovered
			Atropine sulphate	0·006–0·05	0·029	
Moderate	32	1 3/12–4 2/12 (2 6/12)	Diphenoxylate Hydrochloride	0·25–8·4	2·3	Recovered
			Atropine sulphate	0·002–0·084	0·023	
Severe	4	10/12–2 1/12 (1 8/12)	Diphenoxylate Hydrochloride	0·77–10·0	4·7	1 Died 3 Recovered
			Atropine sulphate	0·007–0·10	0·047	

*Age and amount ingested not known in one patient.

(Wasserman, 1974). Its safety for young children, however, is open to question. While the amount of atropine sulphate is very small for the adult patient, children can develop atropinism even with normal dosage (Wasserman *et al.*, 1975). Furthermore, in children there is a very narrow range between therapeutic and toxic dosage and they may exhibit an intolerance to the drug (Bovier-Lapierre *et al.*, 1973; Scorza *et al.*, 1974). We were unable to find a correlation between the severity of symptoms and the dose ingested. Because of this it is not possible to predict what dose will be toxic in children, and while some may have only the mildest symptoms with relatively large doses, others develop severe toxicity on ingesting an amount near the normal dose. In our series in each group of poisoned patients there were children who had ingested small and some who had taken relatively large amounts of the drug (Table 2). Furthermore, analysis of reported cases of Lomotil intoxication confirms the absence of any relationship between the ingested dose and the intensity of subsequent symptoms (Table 3). This is also evident in considering the fatal cases where one patient succumbed to a dose of 5·6 mg/kg diphenoxylate, while the patient cited by Ginsburg and Angle (1969) ingested only 1·3 mg during a 24-hour period. Because of its action in rendering the gut atonic, Lomotil is slowly absorbed once peak plasma levels are reached (at 2 hours) and its excretion is prolonged by an enterohepatic circulation (Karim *et al.*, 1972). Therefore delay in onset and recurrence of symptoms are both features of overdosage (Henderson and Psaila, 1969; Riley, 1969; Wheeldon and Heggarty, 1971). Because of the difficulty in predicting the clinical outcome, all children who have ingested Lomotil in excess, or who show features of toxicity from therapeutic amounts of the drug, must be admitted for observation for a period of at least 24 hours.

The diagnosis of Lomotil poisoning is not aided by the laboratory as the rapid conversion of diphenoxylate to diphenoxylic acid renders it undetectable in blood or urine although atropine may be detectable in biological fluids. Our patient who died had traces of atropine in the liver 4 days later, but diphenoxylate was not detectable in any of the biological fluids. Therefore lack of laboratory detection has some major implications for treatment of suspected Lomotil poisoning. However all patients suspected of Lomotil poisoning must have gastric lavage performed, irrespective of the length of time after ingestion and of whether or not emesis has occurred, to ensure maximum gastric emptying (Rumack and Temple, 1974). Activated charcoal may adsorb diphenoxylate and can be left in the stomach in a dose of 2 g/kg (Corby *et al.*, 1970). The administration of an emetic is probably undesirable because of the rapidity with which the patient may become apnoeic and drowsy, thus increasing the possibility of aspiration. Although atropine is removed from the body more rapidly by forced diuresis, this is an ineffective way of increasing diphenoxylate excretion (Way, 1968). Similarly there is no evidence that haemodialysis, peritoneal dialysis, or exchange transfusion will adequately remove significant quantities of diphenoxylate or its metabolites. The appearance of either respiratory depression or drowsiness is the signal for the use of a narcotic antagonist. Naloxone is the drug of choice as it does not cause respiratory depression (Evans *et al.*, 1973). The recommended dose of naloxone is 0·005 to 0·1 mg/kg given intravenously, intramuscularly, or subcutaneously and this dose may be repeated at intervals of 2–3 min according to clinical response. Since its duration of action is much exceeded by that of diphenoxylate it may need to be given frequently as its effect tends to diminish after about 2–3 hours. Therefore overdoses should be treated promptly with gastric lavage, and intensive monitoring of the patient's respiratory and conscious state during the first 24 hours is mandatory.

As in 67% of our cases Lomotil had been prescribed for an adult relative, parents should be instructed to keep the drug out of the reach of

Table 3 *Summary of reported cases of Lomotil poisoning*

Authors	*Year*	*Cases (n=79)*	*Age range (mean)*	*No. of tablets*	*Diphenoxylate*	*Outcome (recovered n=74)*
Harries and Rossiter	1969	1	2 years	12	2·4	Died
Ginsburg and Angle	1969	1	5 years	8½	1·2	Died
Rumack and Temple	1974	16	6/12–4 6/12 (1 9/12)	½–40	0·18–7·4 (2·7)	1 Died 15 Recovered
Wasserman *et al.*	1975	16	7 weeks–6 years (22 months)	2–150 (32)	*	1 Died 15 Recovered
Our series	1979	45	10 months–6¾ years (2 6/12)	2–40 (14)	0·25–10 mg (2·8)	1 Died 44 Recovered

Lomotil one tablet/5 ml contains diphenoxylate 2·5 mg plus atropine sulphate 0·025 mg.
*Details of individual cases not given in the paper.

children and any remaining tablets should be returned to the chemist as soon as the illness is over. Some of our patients took tablets which had been prescribed some time before by the general practitioner. Needless to say, the doctor should prescribe these tablets in limited quantities.

Although the manufacturers indicate that Lomotil is contraindicated in children under age one year, we doubt if it has any place in the treatment of diarrhoea in children.

We are grateful to our colleagues for allowing us to study patients under their care.

Paper given at the Summer Meeting of the Scottish Paediatric Society held at Ninewells Hospital, Dundee, 2 June 1978.

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Foot length—a new and potentially useful measurement in the neonate

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SUMMARY The foot length, occipito-frontal head circumference (OFC), crown-rump, and crown-heel length (CHL) of 123 neonates of gestational ages 26–42 weeks, were measured between 12 hours and 5 days. A gauge, designed and constructed at St Mary's Hospital, Manchester, was used to measure foot length. In term babies (37–42 weeks) who were of weights appropriate for gestational age (AGA) the scatter about the mean of foot length measurements was small (coefficient of variation = 4·5%) compared with birthweight (coefficient of variation = 12·0%). The wide range of foot length measurements in babies of different gestational ages prevented maturity being accurately estimated. The mean birthweight of term light-for-dates (LFD) babies was 30·9% lower than term AGA babies, whereas the mean foot length, OFC, and body length of LFD babies was reduced by only 4·2–8·8%. There was a positive linear correlation between foot length and other indices of body size in LFD and AGA babies of all gestational ages. However, in premature babies (<37 weeks) the correlation between foot length and birthweight (r = 0·95) and foot length and CHL (r = 0·96) was pronounced. The 95% confidence limits of the regression lines were ± 327 g and ± 2·3 cm respectively. Birthweight and CHL of premature babies can therefore be estimated from a measurement of foot length that is performed simply and rapidly. Measurements of foot length are valuable in premature babies who are too ill at birth for conventional anthropometric measurements to be made, and in whom such measurements cannot be carried out subsequently because of the encumbrance of the incubator and intensive care apparatus. Drug dosages and intravenous fluid requirements based on body weight or surface area can be indirectly calculated from a measurement of foot length.

Certain ill newborn babies, particularly those that are premature, require intensive care from the moment of birth. It is rare for measurements such as birthweight, body length, and occipito-frontal head circumference (OFC) to be made because priority is given to life support. It is virtually impossible to gain access to these babies for anthropometric measurements because they are nursed in incubators and attached to monitoring devices, intravenous infusion lines, and often to mechanical ventilators. Yet the dosages of various drugs and intravenous fluid requirements are based on body weight or surface area.

The foot is usually readily accessible for measurement of its length, even in premature babies, nursed in incubators, and receiving intensive care. There is a positive correlation between foot length and height in adults (Dahlberg and Lander, 1948; Helmuth, 1974). Foot length in the fetus is closely correlated with body length (Pospisilova-Zuzakora, 1962) and gestational age (Markowski and Lawler, 1977). We studied foot length measurements in the newborn as a method of estimating other anthropometric indices.

Patients and methods

A neonatal foot length gauge (Fig. 1) was designed by one of us (D.K.J.) and constructed in the hospital workshop (Department of Medical Physics). It is made from Perspex and consists of a platform against which the baby's heel is placed, and a sliding bar which makes contact with the tip of the big toe. The scale beneath the sliding bar has a range from 2 to

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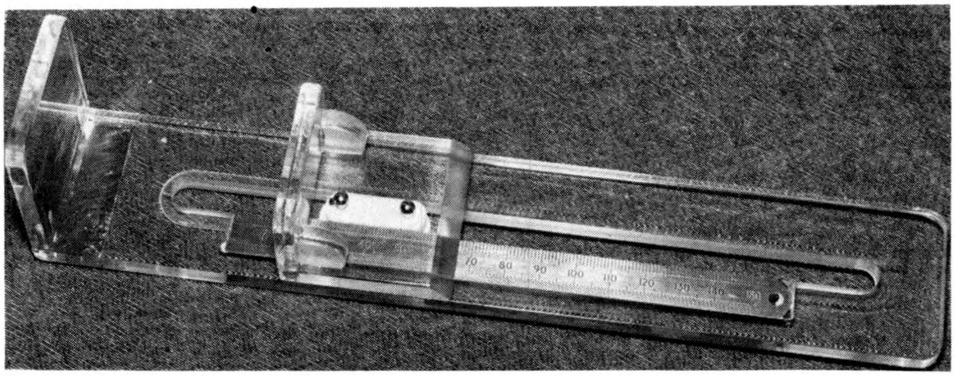

Fig. 1 *The neonatal foot length gauge.*

15 cm and reads to the nearest 0·5 mm. The instrument is small enough to be introduced through the porthole of an incubator within which it is easily manipulated.

The baby's left foot is held in the examiner's left hand and the gauge is held in his right. The heel is placed against the platform and the head of the first metatarsal and medial aspect of the heel are aligned parallel with the edge of the instrument. The index finger of the examiner's right hand manoeuvres the sliding bar until it just touches the tip of the big toe (Fig. 2). The instrument is withdrawn and the scale is read.

Observer error of the method. The left foot of one baby was measured by one of us (D.K.J.) on 10 occasions within 30 minutes. The result (mean ± SD) was 7·62 ± 0·08 cm; the coefficient of variation was 1·05%. The same baby's foot was measured once by 10 different examiners (nursing and medical staff of the special care baby unit). The result (mean ± SD) was 7·56 ± 0·11; the coefficient of variation was 1·46%.

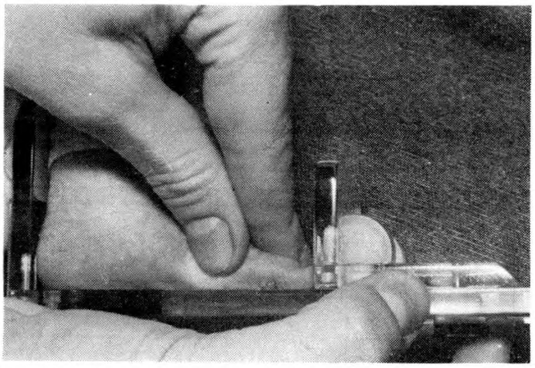

Fig. 2 *The neonatal foot length gauge.*

Measurements were made of foot length (left), OFC, crown-rump, and crown-heel length (CHL) in 123 singleton babies (M:F 59:64), 26–42 weeks' gestation, and of known birthweights. Measurements were made between 12 hours and 5 days. Serial observations previously made suggested that there was no significant change in foot or body length during the first 5 days of life. OFC measurements were made with a glass-fibre tape measure, and body length was measured with the Cardiff neonatometer (Davies and Holding, 1972). Gestational age of each baby was calculated from the first day of the mother's last menstrual period. If this was unknown, clinical examination of the newborn and/or radiological assessment of bone age was used to determine gestational age (Russell, 1969). 66 babies were of weights appropriate for gestational age (AGA) according to the birthweight centile chart of Milner and Richards (1974). 57 babies were < 10th centile for gestational age and were termed light-for-dates (LFD).

Results

In the 94 term (37–42 weeks) AGA and LFD babies birthweight was the index of body size that had the greatest scatter of the results about the mean (coefficient of variation = 12·0 and 11·9% respectively), whereas the coefficients of variation of foot length, OFC, and body length were smaller (3·5–8·5%) (Table 1). Nevertheless, in babies of different maturity there was a wide range of foot lengths at each gestational age and there was a considerable overlap between foot lengths at different gestational ages (Fig. 3).

For each index of body size the mean result in LFD term babies was compared with the corresponding result in AGA term babies and the percentage reduction was calculated. LFD babies

Table 1 *Mean ± SD, coefficient of variation of different indices of body size in 94 term babies who were of weights appropriate for gestational age or light-for-dates. The percentage reduction of mean values in LFD babies compared with AGA babies is also shown.*

Indices	*Babies*				
	Weight appropriate for gestational age (n= 51)		*Light-for-dates (n = 43)*		*Reduction of mean values (%)*
	Mean ± SD	*Coefficient of variation (%)*	*Mean ± SD*	*Coefficient of variation (%)*	
Foot length (cm)	7·92 ± 0·36	4·5	7·24 ± 0·4	5·5	8·6
Birthweight (g)	3402 ± 408	12·0	2350 ± 280	11·9	30·9
Occipito-frontal circumference (cm)	34·03 ± 2·88	8·5	32·60 ± 1·32	4·0	4·2
Crown-rump length (cm)	34·13 ± 1·52	4·5	31·12 ± 1·39	4·5	8·8
Crown-heel length (cm)	51·08 ± 2·05	4·0	46·58 ± 1·61	3·5	8·8

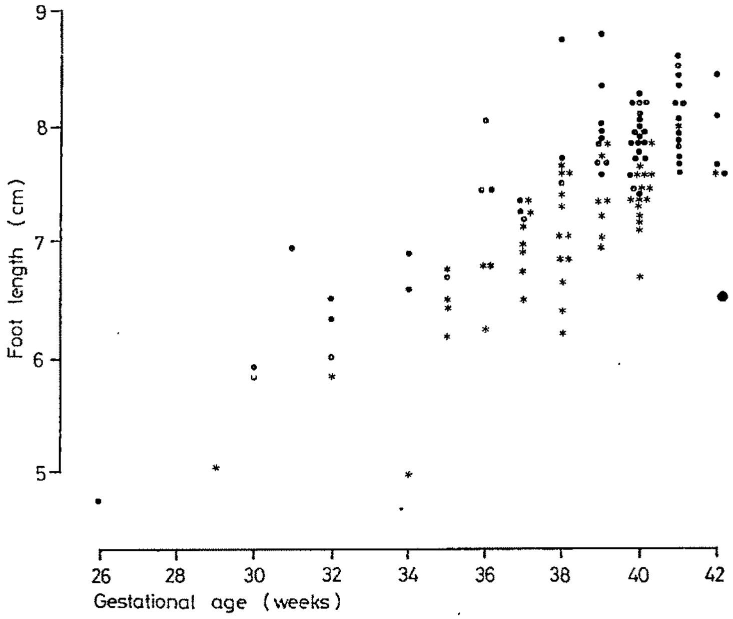

Fig. 3 *Foot lengths of babies of different gestational ages. Weight appropriate for gestational age ●; light-for-dates*.*

were 30·9% lighter than AGA babies. However, there was only a modest reduction (4·2–8·8%) of the mean foot length, body length, and OFC in LFD babies compared with AGA babies (Table 1).

A positive linear correlation between foot length and the other indices of body size was observed in AGA and LFD babies of all gestational ages (Table 2). However, the foot lengths of the 23 premature babies (< 37 weeks) showed an especially high degree of correlation with birthweight (r = 0·95) and crown-heel length (r = 0·96), and the 95% confidence limits of the regression lines were ± 327 g and ± 2·3 cm respectively (Figs 4 and 5).

Table 2 *Correlation coefficient (r) between foot length and other indices of body size in 123 babies, 26–42 weeks' gestation, who were of weights appropriate for gestational age or light-for-dates*

Foot length v. other indices	*Correlation coefficient (r)*	
	Weight appropriate for gestational age	*Light-for-dates*
Foot length		
birthweight	0·89	0·91
occipito-frontal circumference	0·90	0·82
crown-rump length	0·88	0·89
crown-heel length	0·91	0·88

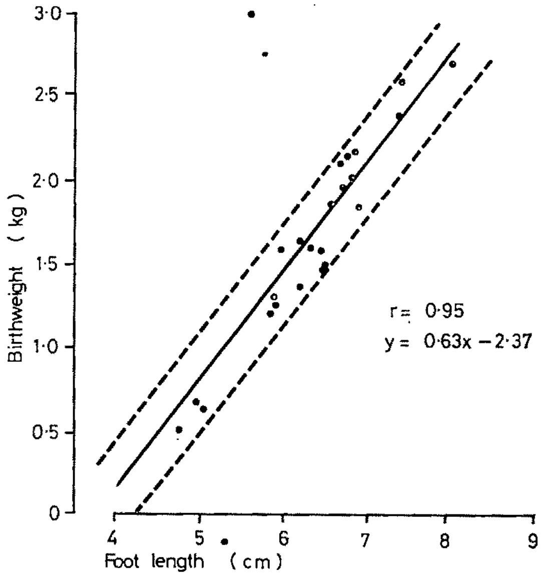

Fig. 4 *Birthweight (kg) and foot length (cm) of 23 premature babies. On either side of the regression line (solid) are the 95% confidence limits, ± 327 g (broken line).*

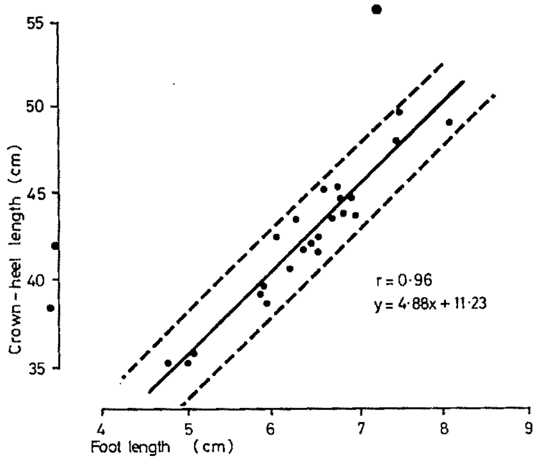

Fig. 5 *Crown-heel length (cm) and foot length (cm) of 23 premature babies. On either side of the regression line (solid) are the 95% confidence limits, ± 2·3 cm (broken line).*

Discussion

Ill newborn babies nursed in incubators and receiving intensive care are generally inaccessible for measurements of bodyweight and CHL. Such babies are usually premature and, as well as requiring intravenous fluids, are potential recipients of a variety of drugs including antibiotics, digoxin, and alkalising agents, the dosages of which are calculated according to bodyweights or surface areas. We have shown that birthweights and CHL of premature babies can be estimated from measuring the foot lengths and such measurements can be made simply, rapidly, and safely in spite of the encumbrance of the incubator and intensive care equipment. In those babies who are so ill at birth that measurements of weights and body lengths are not possible, the measurement of foot length allows fluid requirements and drug dosages to be calculated.

In term babies foot lengths, like body lengths, and OFC had relatively small scatter of results about the mean compared with birthweights. Markowski and Lawler (1977) suggested that foot length could be used to predict the gestational age of very premature aborted fetuses. However, in this study the range of foot lengths at different gestational ages was so wide as to preclude the accurate estimation of maturity.

It is conventional teaching that LFD babies tend to be long and to have large heads in relation to their birthweights. Our findings reinforce this and suggest that in most cases of intrauterine growth retardation foot length is also spared at the expense of bodyweight. Járai *et al.* (1977) drew attention to the heterogenecity of LFD babies and demonstrated that those who suffer from hypoglycaemia tend to have a greater reduction in birthweight relative to CHL compared with normoglycaemic LFD babies. The measurement of foot length may prove to be a valuable adjunct to other anthropometric measurements in the classification of LFD babies; it may be the only measurement that can be conveniently made in ill babies nursed in incubators.

We are grateful for the help of Mr S. Carlisle and the Department of Medical Physics who constructed the neonatal foot gauge.

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The following articles will appear in future issues of this journal:

Red cell aplasia in children. *B. P. Alter and D. G. Nathan.*

A suggested child health clinic form. *R. S. Illingworth.*

Mourning by the family after a stillbirth or neonatal death. *E. Lewis.*

Diagnosis and management of folate deficiency in low birthweight infants. *M. K. Strelling, D. G. Blackledge, and H. B. Goodall.*

New technique for servo-control of arterial oxygen pressure in preterm infants. *I. R. Beddis, P. Collins, N. M. Levy, S. Godfrey, and M. Silverman.*

The spread of Coxsackie B1 infection. *T. W. Hoskins, J. R. Davies, A. J. Smith, K. Collingham, and R. N. Chamberlain.*

Haemorrhage responsive to vitamin K in a 6-week-old infant. *A. M. B. Minford and O. B. Eden.*

Drug metabolism in malnourished children. A study with antipyrine. *M. Homeida, Z. A. Karrar, and C. J. C. Roberts.*

Archives of Disease in Childhood, 1979, **54**, 231–239

Short reports

Mycoplasma hominis

A cause of neonatal meningitis

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SUMMARY Two cases of *Mycoplasma hominis* meningitis in the newborn are described. These infants demonstrate the need to consider *M. hominis* as a cause of neonatal meningitis, especially if the Gram stain is negative, conventional cultures yield no growth, and there is a history of maternal infection. CSF cultures on appropriate medium can quickly confirm the diagnosis.

Neonatal central nervous system (CNS) infection due to *Mycoplasma hominis* has rarely been reported, despite the frequency with which it colonises the newborn (Klein *et al.*, 1969). A review by Remington and Klein (1976) described only 2 patients, and another case was recently reported (Siber *et al.*, 1977). This paper reports 2 more cases and demonstrates the significance of *M. hominis* in the aetiology of neonatal CNS infection, especially when the initial culture is negative.

Case reports

Case 1. The 1·74 kg baby girl of a 37-year-old gravida 5 para 1 mother was delivered at 33 weeks' gestation via forceps after membranes had been ruptured for 5 days. At delivery the mother's temperature was 38·3°C (oral) and although treated with ampicillin her fever persisted for 6 days. The baby was bottle fed and did well for the first 5 days of life but then developed fever (38·8°C rectally). Skin, blood, and suprapubic urine cultures were performed but no antibiotics were given. These cultures were sterile but on the 7th day the WBC was 36 000/mm^3 ($36 \times 10^9/l$) (79% neutrophils and 17% lymphocytes). Fever persisted and lumbar puncture was performed on the 8th day (Table 1). This confirmed the diagnosis of meningitis. IV ampicillin (200 mg/kg per day) and chloramphenicol (50 mg/kg per day) were started, and 1 mg intrathecal gentamicin was also administered. Generalised seizures developed and phenobarbitone was given. On the 9th day (Table 1) 0·5 mg gentamicin was instilled into the left lateral ventricle. At this time a growth of *Mycoplasma* was obtained from the mother's blood culture and the infant was started on IV tetracycline (20 mg/kg per day). Ampicillin was stopped but 2 further doses of intraventricular gentamicin were given. On the 15th day of life (10th day of illness) *Mycoplasma* was isolated from the

Table 1 *CSF results in Case 1*

Age (days)	*Source*	*RBC* ($\times 10^6/l$)	*WBC* ($\times 10^6/l$)	*% polymorphs*	*% lymphocytes*	*Culture*	*Protein* (*g/l*)	*CSF glucose* (*mmol/l*)
8	Lumbar	19 000	19 500			*M. hominis*	7·0	0·5
8	Lumbar	62 000	62 500	91	9	*M. hominis*		
9	Left ventricle	10 000	2 300	92	8	No growth		
10	Left ventricle	1 440	2 000	90	10	No growth		
11	Left ventricle	15 000	2 000	94	6	No growth	2·5	0·8
13	Lumbar	300	1 120	90	10	No growth	7·0	0·9
15	Lumbar	1 800	110	87	13	No growth	6·0	1·3
23	Lumbar	5	14	98	2	No growth	2·0	1·5
36	Lumbar	315	3	—	—	No growth	1·3	2·4

Conversion: SI to traditional units—Glucose 1 mmol/l ≈ 18 mg/100 ml; protein 1 g/l ≈ 100 mg/100 ml.

CSF obtained at the original lumbar puncture. All *Mycoplasma* isolated were later identified as *M. hominis*. Drug sensitivities for the organism are listed in Table 2. Subsequent antibiotic treatment consisted of IV chloramphenicol and tetracycline for a total of 21 days of each drug. There was continued improvement in the CSF and there were no more convulsions after the 10th day of treatment. The baby was discharged on the 40th day of life when neurological examination was entirely normal; follow-up at 9 months showed development to be normal with no evidence of residual neurological dysfunction.

Case 2. A baby girl born at term after an uncomplicated pregnancy and delivery. Birthweight was 4·02 kg. Nine days after birth the mother developed a febrile illness associated with a thick vaginal discharge. She was started on oral ampicillin and septrin, and continued to breast feed the infant who remained well. At 15 days the child became irritable and developed a fever of 38·0°C (rectal). Three days later she developed 'head retractions' and vomiting. She was admitted to hospital at 21 days; she was feeding poorly, febrile, irritable, and had generalised hypotonia. A lumbar puncture confirmed the diagnosis of meningitis (Table 2). Blood and urine cultures were sterile. Peripheral WBC was 26 100/mm^3 ($26·1 \times 10^9$/l) (93% neutrophils). She was started on gentamicin (4 mg/kg per day) and cloxacillin (62·5 mg/kg per day) together with phenobarbitone and hydrocortisone. There was a transient improvement but she deteriorated 2 days later. Antibiotics were changed to ampicillin (250 mg/kg per day) and cloxacillin (250 mg/kg per day). Again transient improvement was noted although CSF showed a persistent heavy pleocytosis. Bacteriological culture of CSF, however, remained sterile. At age 32 days the child deteriorated once again with seizures, pyrexia, and vomiting. She was transferred to The Hospital for Sick Children where repeat lumbar puncture was performed and CSF cultured for *Mycoplasma*. Gentamicin (6 mg/kg per day) was again given and cloxacillin was stopped in favour of chloramphenicol (25 mg/kg per day). Seizures were controlled with phenytoin (7 mg/kg per day) and rectal paraldehyde. Three days later *Mycoplasma* was identified from the CSF and later shown to be *M. hominis*. Oxytetracycline was started (20 mg/kg per day) and chloramphenicol stopped when drug sensitivities were obtained for the organism (Table 3). During the next 2 weeks there was clinical improvement with fewer seizures, good weight gain, and persistent improvement in the CSF. Antibiotics were stopped after 21 days of treatment with gentamicin and tetracycline, the latter being given orally for the last 10 days. At discharge the baby, aged 9 weeks, had normal reflexes, good tone, and was beginning to smile. She remained on anticonvulsant treatment in tapering dosage. Follow-up at age 10 months showed that she was developmentally normal for age, but had clinical evidence of a mild right-sided hemiplegia.

Table 3 *Sensitivities of two strains of Mycoplasma hominis to antimicrobial drugs*

Case	*Ch*	*Ery*	*Gent*	*Tet*	*Clind*	*Amp*	*TMX*
1	S	R	PR	S	NT	R	R
2	R	R	S	S	R	R	R

Ch = chloramphenicol, Ery = erythromycin, Gent = gentamicin, Tet = tetracycline, Clind = clindamycin, Amp = ampicillin, TMX = trimethoprim, R = resistant, PR = partially resistant, = sensitive.

Discussion

M. hominis is known to be a cause of paediatric illness and puerperal sepsis (Stokes, 1955; Klein *et al.*, 1969). The 2 cases described also demonstrate its role in neonatal CNS infection. In Case 1 the organism was not isolated until the 15th day of illness when pinpoint colonies were seen on Columbia blood agar (oxoid) and were grown within 48 hours of transfer to PPLO media (Difco nutrient base with 20% horse serum, 6·6% yeast extract, and ampicillin 1000 units/ml). In Case 2, pinpoint colonies showed the typical 'fried egg' morphology that was described by Siber *et al.* (1977). Growth may also be enhanced by incubation with 10% carbon dioxide

Table 2 *CSF results in Case 2*

Age (days)	*Source*	*RBC* (× 10^6/l	*WBC* (× 10^6/l)	*% polymorphs*	*% lymphocytes*	*Culture*	*Protein* (*g/l*)	*CSF glucose* (*mmol/l*)
21	Lumbar	NR	4 000	100	0	No growth	3·6	
23	Lumbar	2 200	180	80	20	No growth	1·6	
28	Lumbar	NR	1 400	100	0	No growth	1·6	
30	Lumbar	NR	775	100	0	No growth	1·4	
31	Lumbar	450	1 050	55	45	*M. hominis*		2·8
33	Left ventricle	131	156	35	64	*M. hominis*	1·3	1·4
51	Left ventricle	2 500	33	11	89	No growth	0·6	1·7

Conversions as in footnote to Table 1. NR = Not recorded or nitrogen, but neither method was used in these cases. Both patients probably acquired the infection from their mothers and the meningitis was treated in the conventional way once the diagnosis was confirmed but neither responded despite several changes of antibiotics. It was only after identification of *M. hominis* and the institution of appropriate treatment based on the sensitivities of the organism that there was clinical improvement.

We thank Professor Hurley and Dr de Luvois of Queen Charlotte's Hospital, London for bacteriological identification in Case 1, the staff of the Mycoplasma Reference Laboratory for classification of the organisms, Miss J. Robinson and Miss P. Redmond for clerical help.

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A clinical comparison of beclomethasone dipropionate delivered by pressurised aerosol and as a powder from a rotahaler

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SUMMARY 14 children with severe asthma were studied for 2 months in a double-blind cross-over trial to compare the efficacy of beclomethasone dipropionate delivered as an aerosol and as a powder from a rotahaler.* Inhalation via the aerosol was satisfactory in 13 patients, each of whom used the rotahaler correctly. Younger children preferred to use the rotahaler. Comparison of daily symptoms, twice daily peak expiratory flow rate (PEFR), and use of salbutamol during the 2 months of the trial showed that control of asthma was equally good, irrespective of the device used to deliver active beclomethasone.

There have been many studies demonstrating that beclomethasone dipropionate aerosol is safe and effective in the long-term management of severe childhood asthma (Morrow Brown and Storey, 1973; Godfrey and König, 1974; Lovera *et al.*, 1976). However, some children have difficulty using pressurised aerosols correctly, and consequently they have been denied the benefit of this form of treatment. Recently beclomethasone dipropionate has become available in powder form mixed with a lactose base. It is dispensed in capsules which are used in a rotahaler* (Hallworth, 1977). This device requires less co-ordination for effective use as the patient has only to breathe through it to inhale the powder. We have conducted a 2-month double-blind randomised cross-over trial to determine whether beclomethasone dipropionate dispensed in this way is as effective in controlling symptoms of asthma as the usual preparation delivered as a metred dose from a pressurised aerosol. We also tried to find out if there were any problems associated with the use of the rotahaler in paediatric outpatient practice.

Patients and methods

Seven boys and 7 girls (mean age 9·7 years, range 4·8–15·1 years) were studied. They were all asthmatic and had previously been judged on clinical grounds to require treatment with beclomethasone. Before the trial they had been using beclomethasone regularly for a mean period of 1 year 10 months (range 0–5 years 5 months). 11 of them had failed to respond satisfactorily to treatment with sodium cromoglycate and one had failed to respond to treatment with regular theophylline. Two had previously been treated with alternate day oral prednisolone and had subsequently been weaned off this on to aerosol beclomethasone dipropionate. Three patients had required short courses of oral prednisolone during the previous year.

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*Allen and Hanbury's Research Division.

At the start of the trial all the patients were taught how to use both the aerosol and the rotahaler. At the end of the month each child was asked to demonstrate the use of both devices. He/she was given a score out of 10 for use of the aerosol. Droplet escape from nose or mouth, timing of aerosol release during inspiration, and size of breath taken (tidal or full vital capacity) were scored. It was noted whether the child was able to assemble the rotahaler correctly with the capsule in place, whether the powder fell on the floor, and whether he/she made an inspiratory effort great enough to inhale all the powder.

Throughout the trial the patients took two puffs of aerosol 4 times a day and powder from one capsule in the rotahaler 4 times a day. Each month one device contained active drug and the other an appropriate placebo. The order in which the patients received the drugs was randomly assigned by the hospital pharmacist and was not disclosed to the patients or the physicians until the trial was completed. All patients were given a salbutamol aerosol in addition to the beclomethasone to use as necessary for cough or wheeze. During the trial the patients recorded their symptoms each day in a diary card (Connolly and Godfrey, 1970). They also recorded peak expiratory flow rate (PEFR) every morning and evening. This was measured as the best of 3 attempts using a calibrated peak flow gauge (Airmed Ltd). The amount of salbutamol used to treat intermittent symptoms was also noted. Comparison of the results in the two treatment periods was made using paired *t* tests.

Results

Use of inhalation devices. All children were able to use the rotahaler correctly and 13 achieved mean scores of 8 or more for aerosol inhalation technique. Two had not used an aerosol before the trial. One of these had a mean score of 5 for inhalation technique. The Table shows that younger children preferred to use the rotahaler while older ones preferred the aerosol. Although the figures are too few for statistical analysis there did not appear to be any relationship between the length of time of previous beclomethasone treatment and preference for device.

Table *Age of patients, time of previous experience with aerosol, and preferred device (aerosol or rotahaler)*

Age of patient (years)	*Previous duration of aerosol treatment (years)*	*Preferred device*
15·1	1·3	Aerosol
13·8	2·3	No preference
13·7	0·0	No preference
12·8	1·2	No preference
11·9	1·3	No preference
10·7	5·4	Aerosol
10·1	1·3	Aerosol
9·8	2·9	Aerosol
7·3	2·9	No preference
7·1	1·1	Rotahaler
6·9	0·0	No preference
6·0	2·0	Rotahaler
5·8	2·8	Aerosol
4·9	1·1	Rotahaler

Response to treatment. Symptom scores, number of symptom-free days, morning and evening PEFR results, and the amount of salbutamol used were recorded for each month of the trial. The mean symptom score was significantly lower during the month of treatment with active aerosol and placebo powder (P = 0·04), but there were no significant differences between the two periods for any of the other recorded parameters. The child who scored only 5 out of 10 for aerosol inhalation technique was as well in the month that he was taking aerosol as in the month that he was using the rotahaler. Of 8 patients who stated a preference for one type of device only 2 were controlled better during the month they were using that device.

Discussion

This trial has shown that beclomethasone dipropionate delivered from a rotahaler was as effective as that delivered by pressurised aerosol in controlling the symptoms of this selected group of asthmatic children. Most of the patients had been using the aerosol for some time and all but one were given a mean score of at least 8 for their aerosol inhalation technique. Preference for a particular type of device was not related to symptom score or PEFR recorded during the month of its use for active drug. However, the 3 patients who preferred to use the rotahaler were among the younger children in the trial. It is probable that the rotahaler would prove more effective than an aerosol for young children who have difficulty using pressurised aerosols. Provided inhalation is continued until all the powder from each capsule is used, there is far less chance that it will be delivered incorrectly. All our patients were able to use the device without difficulty.

It is concluded that beclomethasone powder delivered from a rotahaler is a useful addition to the therapeutic armoury for the management of severe asthma in childhood.

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Cefuroxime plasma and CSF levels in children with meningitis

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SUMMARY Cefuroxime (25 mg/kg) given intravenously every four hours to 7 children with bacterial meningitis resulted in satisfactory therapeutic blood and CSF levels. All children made a full recovery and side effects were absent.

Bacterial meningitis in children carries a 10–15% mortality rate and there can be significant neurological damage in children who recover (Goldacre, 1977). The success of any antibiotic in the treatment of this disease depends on its antibacterial properties and the concentration that remains in the blood and CSF after systemic administration. Unfortunately, during the last few years, sulphonamide-resistant meningcocci have emerged (Lambert, 1974), *Haemophilus influenzae* is now sometimes resistant to ampicillin because of β-lactamase production, and meningitis due to chloramphanicol-resistant *H. influenzae* has recently been reported (Kinmonth *et al.*, 1978). Therefore, triple treatment with a sulphonamide, ampicillin, and chloramphenicol is often used before the causative organism is known. Cefuroxime, unlike the other three agents, is highly active against all the organisms that commonly cause meningitis—namely *Neisseria meningitidis*, *H. influenzae*, and *Streptococcus pneumoniae* (O'Callaghan *et al.*, 1976). It was felt appropriate, therefore, to determine blood and CSF levels of cefuroxime in children with meningitis before this antibiotic was considered as an alternative treatment.

Patients, methods, and results

The treatment currently used at this hospital for children with meningitis consists of ampicillin (25 mg/kg), chloramphenicol (15 mg/kg), and sulphadimidine (25 mg/kg), by IV infusion every four hours for a period of up to 5 days. Treatment is modified depending on the sensitivity of the organism to these agents, and then it is continued orally for an additional period of 5 days.

Cefuroxime (25 mg/kg) was given intravenously by a 20-minute infusion every four hours to 7 children (6 boys; age range, 1½–6 years) for periods of between one and 5 days in addition to the above treatment. The organism responsible for the meningitis in 3 children was *N. meningitidis* (all resistant to sulphadimidine), and in the other 4 it was *H. influenzae*. Sensitivity testing showed that all the isolated organisms were highly sensitive to cefuroxime. Blood samples were taken twice during treatment and plasma levels of cefuroxime were determined between 30 and 90 min and 4 hours after injection. CSF levels of cefuroxime were measured in 3 patients in whom lumbar punctures were clinically indicated; one child with CSF pressure had lumbar punctures performed 2 hours after a cefuroxime injection on 4 consecutive days. All samples were analysed by a high-pressure liquid chromatography method which enabled cefuroxime to be determined in the presence of other drugs.

Plasma levels of cefuroxime (Figure) determined at between 30 and 90 min and 4 hours after IV infusion

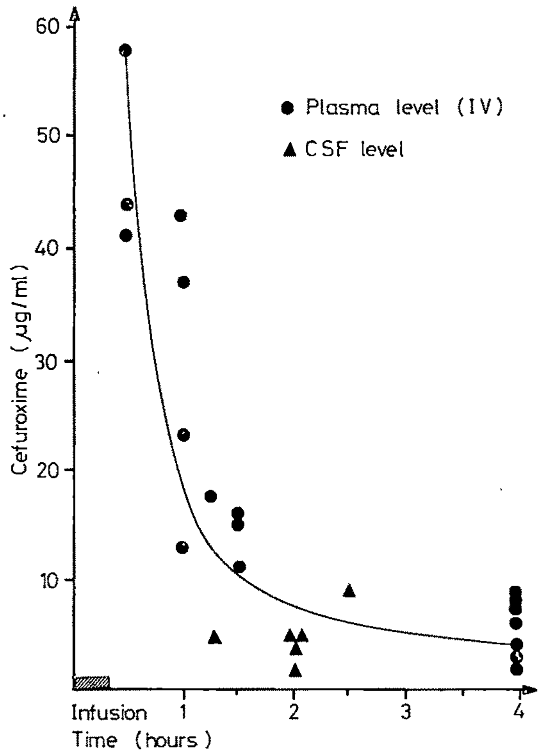

Figure *Plasma levels of cefuroxime in children with meningitis.*

showed that adequate blood levels were obtained and maintained throughout the treatment period. In 3 children the concentration of cefuroxime in CSF was determined and found to be between 1·5 and 9 µg/ml.

Comment

Satisfactory therapeutic blood and CSF levels of cefuroxime are obtained in children with bacterial meningitis, if a dose of 25 mg/kg is given by IV infusion every 4 hours. CSF levels were several times higher than the MICs for *N. meningitidis* (0·025 µg/ml) and *H. influenzae* (0·5 µg/ml). No toxic side effect was noted and all the children made a good recovery. Although one patient was treated successfully with cefuroxime alone after the first day on triple therapy, further clinical studies with cefuroxime are needed to determine whether this new cephalosporin should become a first-line treatment of bacterial meningitis.

We thank Mr John Ayrton of Glaxo Research Limited for the cefuroxime analyses.

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Idiopathic hypoparathyroidism with extrapyramidal and myopathic features

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SUMMARY A case of idiopathic hypoparathyroidism and basal ganglia calcification with extrapyramidal motor and myopathic features is described. The extrapyramidal motor and myopathic features disappeared when normocalcaemia was restored with treatment, suggesting that they resulted from hypocalcaemia.

Idiopathic hypoparathyroidism is an uncommon disease of childhood in which the typical neuromuscular disorders are tetany, fits, and mental retardation. Extrapyramidal and myopathic features have only rarely been described.

Case report

A 12-year-old boy presented with a 2-year history of sudden episodes of generalised tingling, followed immediately by uncontrollable muscle spasms with his limbs assuming bizarre postures, occasionally resulting in his falling to the ground. The episodes occurred 2 or 3 times a week and appeared to be more severe and more frequent after exercise.

He was the only child of healthy unrelated parents. His early growth and development had been normal. When aged 3, he was noted to have an abnormal gait attributed to coxa vara; there was some improvement with treatment, but he continued at times to walk stiffly on tiptoe. His parents felt that for 2 years he had lacked drive, but his school performance had remained satisfactory.

On examination, he was an intelligent boy of normal stature with no dysmorphic features. He had a mask-like facies, exhibited a poverty of movement, and walked with a slow stiff gait; he had strikingly increased muscle tone in all limbs without muscle wasting, tenderness, or weakness; deep tendon reflexes were diminished; he had difficulty in performing rapid repetitive movements, but he was not ataxic and had no sensory deficit. Chvostek's sign was positive and he exhibited chronic carpo-pedal spasm.

Investigations. Plasma calcium 1·37–1·83 mmol/l (5·48–7·32 mg/100 ml), phosphate 2·49–2·87 mmol/l (7·7–8·9 mg/100 ml), magnesium 0·66–0·70 mmol/l (1·6–1·7 mg/100 ml), albumin 44–49 g/l (4·4–4·9 g/100 ml), alkaline phosphatase 183–272 IU/l; urine calcium excretion 0·15 mmol/24 h (6 mg/24 h), phosphate excretion 10·21 mmol/24 h (0·32 g/24 h). Serum parathormone (PTH) 50 pg/ml (normal 250–680), serum 25 hydroxycholecalciferol 27·5 μg/ml (normal 5–30). Plasma creatine kinase (CPK) 13·0 μmol/ml per hour at 37°C (normal 0·25–3·6), alanine aminotransferase 23 IU/l, aspartate aminotransferase 22 IU/l. An Ellsworth Howard test showed a phosphaturic response to PTH. ECG showed a prolonged QTc of 0·49 seconds. An *x*-ray of skull was normal, but computerised axial tomography (CAT) showed dense calcification in both lentiform and caudate nuclei and in both cerebral hemispheres (Figure). EEG showed an excess of large amplitude slow activity without localising or paroxysmal features.

Blood count, ESR, blood urea and glucose, plasma electrolytes, creatinine, bilirubin, immunoglobulins, cortisol and ACTH, serum thyroxine and TSH, urine analysis, urine amino-acids, and faecal fat excretion were normal; no autoantibodies were detected.

A diagnosis of idiopathic hypoparathyroidism was made and treatment was started with dihydrotachysterol (DHT), with calcium and magnesium supplements, and aluminium hydroxide. There was a rapid response to treatment with complete relief of symptoms and signs when the plasma calcium rose above 1·9 mmol/l (7·6 mg/100 ml). Maintenance therapy with DHT 0·5 mg daily continues and the patient remains well.

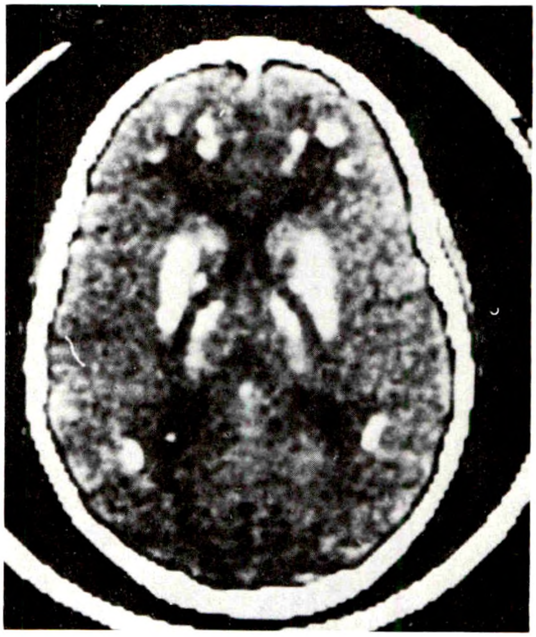

Figure *CAT showing dense intracranial calcification which was not apparent on skull x-ray.*

Discussion

The patient had idiopathic hypoparathyroidism and basal ganglia calcification demonstrated by CAT. He exhibited extrapyramidal motor manifestations, in part related to exercise, which disappeared when normocalcaemia was restored. He also exhibited increased CPK activity to a level associated with myopathy which returned to normal when normocalcaemia was restored. While basal ganglia calcification will be seen more easily in the future by CAT, and therefore may be found more often in idiopathic hypoparathyroidism in childhood, extrapyramidal motor manifestations and raised CPK activity are both rare and do not appear to have been described previously in association with this condition.

Muenter and Whisnant (1968) reviewed the association between extrapyramidal motor manifestations and basal ganglia calcification, and found that the neurological deficit was usually reversible when the patients with hypoparathyroidism were treated.

Tabaee-Zadeh *et al.* (1972) reported a patient with paroxysmal kinesogenic choreoathetosis and basal ganglia calcification due to idiopathic hypoparathyroidism, in whom the extrapyramidal motor features improved when normocalcaemia was restored. They suggested that the movement disorder might be due to a direct effect of hypocalcaemia on already damaged neurones.

Hower *et al.* (1974) described a child with myopathy and idiopathic hypoparathyroidism with increased CPK activity which returned to normal with treatment. They suggested that hypocalcaemia led to lowered cell membrane potentials resulting in increased cell membrane permeability allowing the escape of cytoplasmic proteins.

The findings in this patient suggest that the extrapyramidal motor features were not due directly to the basal ganglia calcification, but that both they and the increased CPK activity resulted from the effects of hypocalcaemia on cell membrane potentials of neurones and muscle.

I am grateful to Dr D. B. Grant for advice and for permission to describe a patient under his care, and to Dr R. D. Hoare for the CAT scan.

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Half life of theophylline in the preterm baby with apnoeic attacks

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SUMMARY Plasma theophylline levels were measured by an enzyme immunoassay method in 6 preterm babies. The method gave accurate and rapid results. The study showed a considerably prolonged half life of an oral preparation.

Xanthine derivatives have become established as a method of treatment of recurrent apnoeic attacks in the preterm baby (Lucey, 1975). However, because of the interpatient variation and prolonged half-life of theophylline in such babies (Giacoia *et al.*, 1976), it is essential that plasma levels be estimated frequently so that adequate doses of the drug can be maintained and serious side effects avoided.

We used an enzyme immunoassay method (EMIT, Syva) for determining plasma theophylline levels on as little as 10 μl plasma. It was known that plasma concentrations measured by either high pressure liquid chromatography or EMIT showed excellent agreement (Chang and Bastiani, 1977).

Patients and methods

Six preterm babies were studied. Details of gestation periods and birthweights are given in the Table. After one attack of apnoea lasting at least 25 seconds, a single oral theophylline preparation was given by a nasogastric tube (theophylline BP as sodium glyconate salt 5 mg/kg). Plasma theophylline levels (μg/ml) were measured at 0, 2, 4, 8, 12, 24, and 48 hours. If a baby had a second attack of apnoea during the period he was withdrawn from the study.

Plasma theophylline levels were estimated by enzyme immunoassay using the EMIT-aad kit

Table *Details of the 6 preterm babies*

Case	*Age (days)*	*Birthweight (g)*	*Gestation (weeks)*	*Theophylline half life (hours)*
1	3	1370	31	35
2	5	2500	36	33
3	11	1400	31	25
4	2	1030	28	64
5	3	2240	37	32
6	12	1950	34	24

(Syva). Volumes of 10 μl plasma were pipetted into microsample cups and thereafter dilutions, reagent additions, and reaction kinetics were performed on the Gilford 3500 analyser in accordance with the manufacturer's instructions for this assay. Under these conditions, neonatal plasma, to which known amounts of theophylline were added, gave coefficients of variation between expected and measured concentrations ranging from 6·5% at 2 μg/ml to 5·5% at 10 μg/ml; values which are compatible with the reported between-run precision of the assay itself.

Results

Peak plasma levels occurred between 4 and 8 hours after the single oral administration of theophylline. The slope of the log of the plasma concentration in the postabsorptive phase plotted against time was used to determine the half-life of the drug. The theophylline half-life for each baby is shown in the Table. The range was 24–64 hours.

Comment

The enzyme immunoassay method for measuring plasma theophylline levels by using microsamples in this group of preterm babies was found to give accurate, reproducible, and rapid (within 10 min) results, thus allowing theophylline dosage to be regulated as often as is clinically indicated. The study showed the prolonged half life of an oral theophylline preparation and the wide interpatient and within-patient variations.

EMIT reagents were kindly donated by Syva Corp. and the 3500 analyser lent for laboratory evaluation by Gilford Instruments Ltd. The oral theophylline was prepared by McCarthy's Pharmaceuticals.

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Archives of Disease in Childhood, 1979, **54**, 240–245

Correspondence

Sodium valproate and pregnancy

Sir,
We were presented with a baby born to a mother taking sodium valproate who wished to breast feed. There are no data on breast milk levels of sodium valproate; it is presumed from collateral evidence that some of the drug would pass across from maternal serum into the milk. Studies in animals given modest doses of sodium valproate during pregnancy (30–90 mg/kg) showed no significant teratogenic effects. When a much higher dose was used (about 600 mg/kg) there was a dose-related increase in the rate of intrauterine death and major fetal abnormalities, most of which involved the kidneys or the lower lumbar spine (Whittle, 1976).

Information on the outcome of the pregnancies where sodium valproate has been taken as the main anticonvulsant is very scanty; in most reports two or more drugs have been used or, in the case of an abnormality, the family history has suggested a strong genetic element (W. Reckitt-Labaz, 1978, personal communication).

Case 1, a 22-year-old primipara, was epileptic and changed to sodium valproate in November 1975. She was well controlled taking 1600 mg/day in divided doses. She had had irregular periods and did not realise that she was pregnant until she was about 14 weeks. She consequently booked at the hospital clinic at about 18 weeks. Her anticonvulsant drug was not changed.

She was admitted in labour at term in July 1978 and delivered a healthy boy weighing 3010 g; Apgar score was 9 at one minute, and no abnormalities were observed. The baby breast fed well and was discharged home on the 6th day, slightly under his birthweight. Mother and baby were seen at 29 days after delivery. The baby was still breast feeding well, gaining weight, and beginning to smile.

The sodium valproate level was measured in the mother's serum, as shown in the Figure. The level fell slightly at term without any change in the oral dose and then rose to the previous level by 29 days. The valproate level in the serum of the neonate was of the same order as that of the mother's at delivery, but fell to insignificant levels by 5 days and was undetectable at 29 days (Figure). The mean level of valproate in breast milk at 5 days was 50 mmol/l; it had fallen to 21 mmol/l by 29 days.

The neonatal valproate level indicates that valproate crosses the placenta freely and maternal serum levels will reflect fetal serum levels. Sodium valproate crosses through from serum into breast milk and will be found at a level between 5 and 10% of that in the mother's serum. The absorption of valproate from breast milk by the neonate appears to be insignificant. In this instance there was no evidence of any abnormality associated with the use of this drug.

It may be concluded that breast feeding while on therapeutic doses of sodium valproate is safe and will not result in detectable neonatal blood levels. Nevertheless, in early pregnancy it must still be prescribed with caution until there is evidence of its safety.

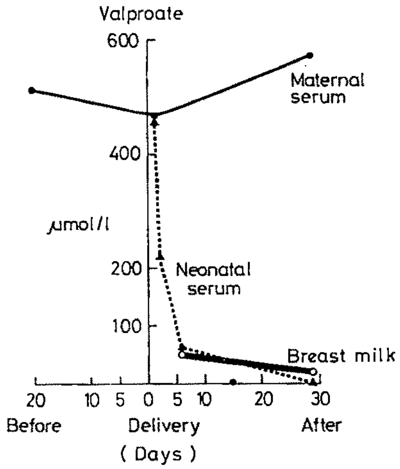

Figure *Maternal serum and breast milk levels of sodium valproate, note marked fall in neonatal serum levels.*

Reference

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Breast feeding and smoking

Sir,
Success at breast feeding has been related to social class (Martin, 1978) and the age at which the mother finished full-time education (Last, 1978; Martin, 1978; Pursall *et al.*, 1978). This study was aimed at determining the prevalence of breast feeding in Cambridge, after delivery and at 3 months. The influence of smoking by mothers was also examined. Smoking by the mother has been shown to have adverse effects on the fetus (Butler *et al.*, 1972) and smoking by either parent an adverse effect on the health of the infant (Leeder *et al.*, 1976), but its effects on lactation do not appear to have been investigated.

330 women delivered consecutively at the maternity hospital in Cambridge in 1978 were questioned after delivery and again at 3 months. The overall prevalence of breast feeding after delivery was 82% and at 3 months' postpartum it was 46%. Initial choice of infant feeding was influenced by social class, with 86% of women from the nonmanual classes starting by breast feeding compared with 76% of manual class women.

The Table compares the prevalence of bottle feeding from delivery, bottle feeding at 3 months by those who began by breast feeding, and breast feeding at 3 months in smokers and nonsmokers. Smokers were less likely to attempt breast feeding than nonsmokers, and this achieves statistical significance in the group overall ($\chi^2 = 6\cdot752$, $P<0\cdot01$) and the manual classes ($\chi^2 = 6\cdot389$, $P<0\cdot02$). Furthermore mothers who smoked and began by breast feeding were more likely to have changed to bottle feeding by 3 months than mothers who did not smoke, and this achieves statistical significance in the nonmanual classes ($\chi^2 = 3\cdot894$, $P<0\cdot05$). Comparison of the mothers who began by bottle feeding with those who were breast feeding at 3 months shows that there were more smokers among the bottle feeders in the group overall ($\chi^2 = 15\cdot494$, $P<0\cdot001$) and in both the nonmanual ($\chi^2 = 4\cdot657$, $P<0\cdot05$) and manual classes ($\chi^2 = 5\cdot26$, $P<0\cdot05$).

Table *Maternal smoking and infant feeding*

	Social class	*Total*	*Artificial feeding*		*Changed to artificial feeding by 3 months*		*Breast feeding at 3 months*	
			No.	*%*	*No.*	*%*	*No.*	*%*
Smokers	Nonmanual	18	5	28	6	33	7	39
	Manual	26	11	42	11	42	4	15
Non-smokers	Nonmanual	117	14	12	28	24	75	64
	Manual	69	12	17	37	54	20	29

There were, as might be expected (Capell, 1978), more (27%) smokers among the manual class mothers than among the nonmanual women (13%). The reasons for smokers being less inclined to breast feed and less likely to persist with breast feeding cannot be ascertained from this study. Smoking was not associated with any particular reason for giving up breast feeding. Nevertheless it appears that smoking by the mother is yet another factor which may influence the prevalence of breast feeding.

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Circulating immune complexes in mucocutaneous lymph-node syndrome (Kawasaki disease)

Sir,
The clinical features of mucocutaneous lymph-node syndrome (MLNS) are well established (Kawasaki *et al.*, 1974), but the aetiology is unknown. Fossard and Thompson (1977) described a Japanese child living in England in whom raised levels of circulating immune complexes by the platelet agglutination test were found early in the disease. Total haemolytic complement and C_4 were depressed although C_3 levels were normal.

Recently we have been able to confirm the abnormal immune complex findings in a 9-month-old Caucasian girl with MLNS. She presented with fever, rash, and stomatitis. After 3 days she became irritable and photophobic; the rash became confluent and prominent over the palms and soles. Lumbar puncture and CAT scan were normal, and she showed no response to several antibiotics (erythromycin, fucidin, flucloxacillin, or ampicillin). Two weeks after the onset of symptoms she was admitted to this hospital where she was noted to have an erythema multiforme-like rash, marked cervical lymphadenopathy, stomatitis, nonpurulent conjunctivitis, puffy feet, and tachycardia. The skin at the fingertips had started to desquamate. She was mildly anaemic and had a leucocytosis. IgE was 44 IU/ml (normal) and total haemolytic complement and C_3 levels were also normal (155 and 124% of normal human serum respectively). Immune complexes containing IgG were raised (41·5% inhibition of IgG latex agglutination (Levinsky and Soothill, 1977): normal subjects <20%). Her illness resolved without further treatment and she was well when she was discharged home on the 43rd day.

Many of the clinical features of this disorder—such as arthralgia, rash, and myocarditis with coronary artery vasculitic changes—could well be due to immune complex deposition. However, raised levels of soluble immune complexes have been described in a variety of diseases and it is difficult to decide whether they are the cause or the result of the disease. Isolation and characterisation of the complexes in patients with this disorder may help to establish the aetiology of this strange disease.

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Thermometers and rectal perforations in the neonate

Sir,

The traumatic origin of many 'spontaneous' perforations of the alimentary canal is worthwhile emphasising (*Archives*, 1978, **53**, 824). Two similar patients were reported previously from Great Ormond Street (Young, 1965) and were described at the Royal Society of Medicine. In the discussion that followed an experienced paediatrician commented, 'This seems to explain the reason why I have intermittent bursts of infants with rectal bleeding as, on reflection, this seems to occur each time we have a new batch of nurses in the nursery'. The presumed cause of this bleeding was from mucosal tear caused by the passage of a thermometer to the rectum.

Perforation of the rectum by thermometers or tubes is more common than reports suggest. Stomach tubes can also be implicated as the cause of some of the 'spontaneous' perforations of that organ.

In an article (Young, 1965), the importance of instruction to nurses was emphasised: 'Instruction to nurses on the anatomy of the rectum must be clear, and to take a rectal temperature the thermometer should be inserted into the anal canal and then advanced at an angle of 30° backwards, not straight into the rectum parallel to the cot as one so often sees'.

In the editorial comment on Frank and Brown's paper (*Archives*, 1978, **53**, 824) your experienced paediatricians give no reasons for the perpetuation of the widespread practice of taking temperatures per rectum. Could we have the reasons for continuing this, or a clear statement that it does not have inherent merit and does have a small but definite risk?

Reference

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Estimation of gestational age at birth—comparison of two methods

Sir,

The Short Report by Serfontein and Jaroszwicz (*Archives*, 1978, **53**, 509) in which the method of Robinson for estimating gestational age was compared with that of Dubowitz contains several errors in both methodology and inference.

After regressing the Robinson gestational age on that by the Dubowitz method they state that 'the 95% confidence interval for a single estimation of gestational age . . . is + 1 week'. (It is curious that this figure is only given to one significant figure whereas the slope of their regression line has 3 and the intercept 7). Confidence intervals derived from regression lines are smallest at the mean (of X) and increase as X gets further from the mean. It is not possible to give a single figure, in this case ± 1 week, for the 95% confidence limits for a single estimation of gestational age. Furthermore, their figure of ± 1 week looks surprisingly small, even assuming it refers to the confidence limits at the mean. In any case, since the objective was to see if Robinson's method could replace the Dubowitz method, the Dubowitz age should have been regressed on the Robinson age; that is, the regression should have been performed the other way round.

The authors state that the Robinson method compares 'very favourably' with the Dubowitz scoring system. This vague statement is presumably based on the observed correlation between the two sets of gestational ages of 0·85. A correlation of this magnitude means that one method explains less than three-quarters ($0\cdot85^2$) of the variability of the other, which in this context is not especially good. They then say that 'both (methods) were found to be accurate between the ages of 29 and 37 weeks', and it is stated that all the mothers were reasonably sure of the dates of their last menstrual periods. However, definitions of 'accurate' and 'reasonably sure' are not given, and no comparison is presented between the 'true' gestational ages and those calculated by either of the two methods under discussion, so that the assertion about accuracy is unsupported.

A final criticism, concerning the design of their investigation, is that it appears that each assessment was carried out by a different person. If this is so, any inherent differences between the two observers are confounded with differences between the two methods, so that the two effects cannot be separated and it is impossible to make a true comparison.

The question which the authors should be asking is 'Do the two methods give comparable results?' and the degree of comparability which is felt acceptable should be specified. If the answer is 'yes' then it would be reasonable to use the simpler Robinson method instead of the more complicated (but better validated) Dubowitz one. Correlation does not answer this question. We expect two measures of the same thing to be correlated; what we are really interested in is the difference between the gestational ages calculated by the two methods. The simplest approach is to calculate the mean and SD of the differences between the two ages. A paired *t* test can be used to test for any systematic difference between the two measures. A significant result looks likely in this case as most of the points in their figure are below the line of identity. From the SD a 95% confidence interval can be calculated. Alternatively, a regression of the Dubowitz age on the Robinson age could be carried out. Each age by the Dubowitz method could then be compared with its estimate, using the regression equation and the observed and estimated ages compared in the same way as before.

The authors have not established that the Robinson method is a good approximation to the Dubowitz system, and their assertions about the accuracy of the method are unsupported.

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Drs Serfontein and Jaroszewicz comment:

We thank Mr Altman for his interest in our paper, although the points he has raised, some of which are valid, are really minor ones and in no way affect the essence of the study.

Regarding the design of the investigation, at the start of the study a trial assessment was made by both of us in which each used the same method of assessment of gestational age on the same infant and no significant differences were disclosed. For the actual study it was felt that the fact assessments were made by two different observers (one doing only the Robinson technique and the other only the Dubowitz method) would result in greater objectivity. Independence of observation was ensured by the results of one examiner not being made known to the other.

With the term 'reasonably sure' it is meant that these were Cape Coloured mothers who could state definite dates of their last normal menstrual periods, had no bleeding within one month of those dates, and had regular menstrual cycles of 28±2 days, the last period being normal in amount and duration. The first day of the last menstrual period (LMP) was used as the reference day and the expected date of delivery was calculated as 280 days (40 weeks) from that day.

Regarding the statistical model and analysis of our study we reiterate that the Robinson method for estimation of gestational age is only pertinent between 29 and 37 weeks' gestation and it is between these limits that we assessed its value against the Dubowitz method. For this reason a paired *t* test comparing the two methods is undesirable. Should one want to do so it would have to be by means of a 4-fold contingency table with age groupings according to both methods. In this way the same restrictions are imposed upon the Dubowitz method as upon the Robinson method. There is no significant difference between the two methods when compared in this manner.

With respect to the correlation, we should like to point out that a correlation of 0·85 significant at P 0·01 suggests that there is one in 100 chance that this correlation is due to chance factors, i.e. reasons other than that warranted by actual strength of data. What this correlation means is that 67% of a rating on one scale is predicted by the ratings on the other scale, which is very high agreement considering other variables that might also influence the ratio. From any statistical view point this magnitude of correlation, which is also not due to chance, is a high one.

We agree that a spuriously high positive relationship may exist because each infant was subjected to both methods of examination. However, we feel the magnitude of the correlation is strong enough to counter this point. Considering that both the Dubowitz and Robinson assessments are subject to error, a correlation of 0·85 is in fact a *very* good one. Good (positive) correlation means that low values obtained with the Robinson method would also be low with the Dubowitz method and vice versa. Further response to this part of Mr Altman's criticism is hampered by the usage of terms such as 'in this context' which we, for our own part, find vague.

Our statement that 'the 95% confidence interval for a single estimation of gestational age is ± one week' is incorrect. This was due to a misinterpretation on our part of the statistician's results. We should, however, like to point out that the standard error of estimate for the Robinson method when measured against the gestational age as determined by LMP is 1·37 weeks, whereas that for the Dubowitz method is 1·94 weeks.

For these reasons and given the magnitude of correlation with only a small chance factor associated with it, it would seem that the Robinson method is a highly suitable alternative to the Dubowitz method for gestational age between 29 and 37 weeks.

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Oral rehydration in infantile diarrhoea

Sir,

Chatterjee *et al.* (*Archives*, 1978, **53**, 284) prefer a solution containing 50 mmol/l sodium for the oral treatment of children with diarrhoea, instead of the 90 mmol/l recommended by the World Health Organisation (1976). In their study of 39 children they found the two solutions were equally effective for rehydration, but that the solution with higher sodium concentration resulted in somewhat more periorbital oedema and hypernatraemia. This difference was not, however, statistically significant and the problems were not shown to have clinical importance. The investigators rehydrated the children using an intragastric drip.

We successfully treated a large number of children from 2 months of age upwards with the solution recommended by the WHO. We normally give the solution as a drink, when the children's thirst controls the amount they take in, and we have found no problems with salt overload. Only in the relatively few children given the solution by intragastric drip for specific reasons (most commonly stomatitis, prostration, or excessive vomiting), have we sometimes encountered periobital oedema among the children a few months old, but this did not appear to influence recovery.

We agree with the generally accepted practice that the oral solution should normally be given as a drink. This is not only pleasanter for the child, but it is the only method suitable for mass use in developing countries, where shortages of trained staff and equipment will generally be much greater than in the conditions of the study in the Calcutta Medical College Hospitals. This method also allows for the close collaboration of the mother in her child's treatment with its potential for health education; and evidently it may be safer.

The common problem in poor conditions with inexperienced mothers and lack of staff is not overhydration but that the child will be given insufficient fluid. In these conditions the solution of higher sodium content is more practical since the volumes needed are less. Additional free water is neither necessary nor recommended. In Mozambique the national policy (Melamed and Segall, 1978) is to use the solution recommended by the WHO.

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Dr Chatterjee and co-workers comment:

We thank Dr Vinhas *et al.* for some very pertinent comments on our paper on oral rehydration in infantile diarrhoea. They treated a group of children with diarrhoea with the oral solution recommended by the WHO and did not have any significant problems of salt overload. Furthermore, they administered the fluid as a drink, except in a few cases where a nasogastric tube was used. We preferred the use of a nasogastric tube for the following reasons: (1) we studied only those children with moderate and severe dehydration; they were very sick and were not well enough to drink, and rapid rehydration was mandatory; (2) as this was a controlled clinical trial, use of a nasogastric tube was preferred to reduce the variability in fluid administration, and (3) aspiration of stomach before administration of fluid, particularly in infants who received loads of antidiarrhoeal medicines before admission, reduces the chance of vomiting. Vomiting is also less likely if the child sleeps while receiving the fluid through a nasogastric tube and is not disturbed to take the drink. We agree that for mass use, if rehydration can be started early, fluid given as a drink is the method of choice and the use of a nasogastric tube should be limited to severely dehydrated infants in cases where quick rehydration is necessary.

The question of salt overload needs a detailed analysis. Although Dr Vinhas *et al.* did not mention the severity of the dehydration, we assume that most of the children had milder dehydration as they were well enough to drink. Even so, while attempting adequate hydration in a few of the severe cases through a nasogastric tube with the solution recommended by the WHO, periorbital oedema occurred in some of them. According to Dr Vinhas, in children receiving the oral fluids by mouth, amelioration of thirst limits the intake. In our experience, however, this is not always so and on many occasions the children continued to drink excessive amounts and developed periorbital oedema. It is pertinent to mention that the estimated episodes of diarrhoea in Asia, Africa, and Latin America in 1975 is 348·2 millions in children aged under 2 years (Rohde and Northrup, 1976). Therefore, if hypernatraemia occurs even in one in a thousand, it will lead to a problem of salt overload in an enormous number of children. We strongly feel that a recommended oral fluid for mass use in the field where supervision is inadequate, should have a higher margin of safety and that the low sodium solution being equally effective should serve this purpose.

Reference

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Prophylactic diazepam in febrile convulsions

Sir,

We read with interest the paper by Knudsen and Vestermark (*Archives*, 1978, **53**, 660) shedding some new light on an old controversy about preventing febrile convulsions (FC). The authors stated that: (1) continuous treatment with phenobarbitone had no advantage over intermittent diazepam; (2) the administration of diazepam was not optimal, so that 80% of children received it too late; (3) diazepam is safe, quickly absorbed, free from undesirable side effects, and, unlike phenobarbitone, is subject to little parental resistance; (4) diazepam may be an alternative prophylaxis of FC, but further controlled investigations are needed.

We performed such an investigation in 1973–75 and checked the results in 1977 (follow-up 18–52 months).

We suggested that parents, after the first FC, should give diazepam (0.6–0.8 mg/kg per 24 hours orally, in 3 doses) at the first sign of illness continuing to the 2nd day after complete recovery. In 1977 we interviewed the parents of 101 children recalled for control and checked all records of readmissions for a new FC or other illness. Of these, 90 had had febrile episodes after the first FC and met the criteria for intermittent prophylaxis: 48 received diazepam by the method and in the doses suggested, 42 did not. The FC recurrence rate in the 'bad compliance' group was 48%, in the 'good compliance' group it was 4% (Dianese and Faccioli, 1979).

The conditions for an effective intermittent prophylaxis of FC with diazepam must be to give the drug in sufficient dosage and to give it in time. Is this feasible? We asked each mother of 100 children (aged between 6 months and 6 years; 45 boys and 55 girls) if she was able to realise that her child was unwell at least 6 hours before the actual fever occurred. In 86% of cases the mother said she was. The symptoms are often trivial, personal, and not 'scientific' in nature, but they are useful in giving to the mother the signal for starting the administration of diazepam. After this preliminary study our policy is now (1) immediate administration of diazepam in clearly stated doses (0.6–0.8 mg/kg per 24 hours in 3 doses) at the first sign of impending illness, continuing for 2–3 days after complete recovery (this regimen is maintained until age 5 years); (2) instruction of all who are concerned with the child, and ensuring the constant availability of the drug. Is this too heavy a commitment for the parents? We do not think so. We are now finding that parents are increasingly willing to comply, provided that the doctors spend sufficient time explaining the aim and benefits of this policy and reassuring them about the safety of the drug, as even unnecessary administration of it for a few days is better than a new FC. Further and more controlled studies are needed. The continuous and adequate treatment of epilepsy precipitated by fever is, of course, mandatory.

Reference

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Orojejunal feeding in low birthweight infants

Sir,

In transpyloric feeding of neonates the use of a silastic catheter by the technique first described by Rhea *et al.* (1973), and recently improved by Della Pietra *et al.* (1978), avoids the risks due to stiffness of the tube but it has the disadvantage that it often takes a long time to pass the catheter into position. We describe a modification to this technique which allows the tube to be positioned in the jejunum more quickly. We insert the catheter through the mouth, but the nasal route may be used equally well.

Materials. (1) A silicone rubber tube 0.63 mm inner diameter, 1.19 mm outer diameter (Silastic Dow Corning), is cut at 55 cm and its end inserted in to (2) a stainless steel plug 7 mm in length, 3 mm outer diameter, with a central canal 0.8 mm in diameter. (3) A small silastic collar is inserted around the neck of the plug to prevent the silastic tube being disconnected from the plug. (4) A PVC tube (K31 Pharmaseal) and (5) a 0.5 mm rigid nylon thread are cut to lengths of 28 cm. Their diameters are such that the silastic tube can be inserted loosely into the PVC tube and also entered easily by the nylon thread. Tubes (1) and (4) are lubricated with vaseline.

Procedure. The silicone tube (with its nylon thread) and the PVC tube are passed through the mouth and oesophagus into the stomach. With the patient now in a horizontal position and on his right side, the tube is pushed some centimeters deeper and passes easily into the duodenum, as shown by the greenish colour and alkaline pH of the aspirated juice. Once the plug is placed in the duodenum, the PVC external tube is withdrawn gently 2–3 cm at a time while the silicone tube is left in place or lightly advanced. This manoeuvre is helped by the stiffness of the silicone tube with the rigid thread inside. Withdrawal of the PVC tube is continued until its distal end reaches the lower portion of the oesophagus. To avoid pushing the silastic tube too far into the jejunum, it should not be inserted more than two-thirds of the glabella-heel distance. After fixing the PVC tube to the side of the mouth the nylon thread is withdrawn and the silastic tube connected to the infusion apparatus. Radiological localisation of the plug is seldom needed.

We have used this technique to feed 48 premature infants with birthweights between 700 and 1500 g (mean 1083) and gestational ages between 25 and 34 weeks (mean 28), in conjunction with nasal CPAP. In each case the duodenum was easily entered, the procedure requiring 10 to 20 min. No perforation or intussusception occurred (Boros and Reynolds, 1974; Chen and Wong, 1974).

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Archives of Disease in Childhood, 1979, **54**, 246–247

Book reviews

Development Defects and Syndromes. By M. A. Salmon and R. H. Lindenbaum. (Pp. 432; illustrated + tables. £30.00 hardback.) HM + M Publishers: Aylesbury. 1978.

The paediatrician or clinical geneticist in search of a syndrome to fit his patient has recourse to a substantial and still growing library of 'syndrome books', for which he is eternally thankful. These have originated almost exclusively from the USA and include Smith's *Recognizable Patterns of Human Malformation*, Bergsma's *Birth Defects Atlas and Compendium*, McKusick's *Mendelian Inheritance in Man* among others. A British addition to this library must therefore be welcomed but, at the same time, it must be judged by the standards set by the earlier American texts. Dr Salmon has assembled information on more than 200 congenital defects and syndromes, with high quality illustrations of most of them. In the first 13 chapters the syndromes are grouped according to the system mainly affected. The last two chapters, on chromosomal syndromes, and an appendix on dermatoglyphics, occupy one-quarter of the book and are Dr Lindenbaum's contribution. There are additional appendices on pedigree symbols and some physical measurements of children.

For each syndrome is given a brief historical bibliography, detailed clinical features and, in most instances, a note on genetic or other aetiological factors. There are some notes about treatment, but this book is designed to help with diagnosis, not with clinical management. Even for genetic counselling, apart from the sections on chromosomal syndromes, the information given is often oversimplified and, occasionally, frankly misleading.

In practical use, the layout of the book is less than ideal. The order of syndromes within sections appears haphazard. The index is a challenge. The reader soon finds that the syndromes are indexed under S rather than under their initial letters, but multiple page references (there are 44 to cleft-palate) are unhelpful. Multiple small errors of omission and commission, in both matter and presentation, spoil what is potentially a very useful book.

I am sorry to have to write critically of a book which is for the most part good, and which represents an enormous investment of labour, However, the truth is that this first edition is not in the same class as its competitors, and at £30 it needs to be. The expenditure of a little more time and a lot more care should make the 2nd edition a winner.

R. W. SMITHELLS

Malignant Diseases of Infancy, Childhood, and Adolescence. Major Problems in Paediatrics, Volume 18. By A. J. Altman and A. D. Schwartz. (Pp. 531; illustrated + tables. £20.00 hardback.) Holt-Saunders: Eastbourne. 1978.

This book is one of a series on Major Problems in Clinical Paediatrics, which aims at providing the general paediatrician with an introduction to the problem of cancer in children, its epidemiology, diagnosis, and management. The book gives good review of the principles of chemotherapy, radiotherapy, the immunology of malignant disease, and the attempts at immunotherapy. Each chapter in the second part of the book deals with a major malignancy. The psychological effects of these diseases and their treatment on the child and the family are discussed. Some of the advice given, while appropriate for the American family and child with malignancy, will need to be modified for this country.

The book is very readable with a clear concise style, up-to-date information—even 1977 references are quoted—and good illustrations. There are some outstanding chapters; one deals with the metabolic haematological, neurological, and infectious complications of malignancy. The section on infections is first class and valuable. It is particularly good because it deals with problems that are likely to be seen in children when they first present or which may complicate their illness after they have left hospital. The subject is rarely considered in other oncology textbooks and was one of the features that convinced me that this was not just another book on tumours, but one that would be of help, not only to
general paediatrician, but to t
specialising in the management of t
conditions.

J. S. MAL

Manual of Emergency Pediatrics. Sec
edition. Edited by R. M. Reece (Re
Chamberlain). (Pp. 721; illustrate
tables. £10.75 soft cover.) Holt-Saund
Eastbourne. 1978.

This book, written by Reece and
contributors, is intended for the paedia
emergency department as a guide
medical and surgical care of sick
injured children. There are 4 secti
true emergencies, presenting compla
(signs and symptoms), diagnostic entit
and procedures and therapeutics. It
difficult to understand this division
should have thought that such things
neonatal gastric perforation, intussusc
tion, volvulus, foreign bodies in
airway, trauma to the urinary tract,
rabies might be considered t
emergencies rather than diagnostic entit

The treatment of cardiorespirat
arrest is well done and would be hel
to inexperienced doctors. It is sad that
cannot be said about the greater par
this book. Experts in different fi
would not refer to it and the inex
would find little of practical use in
mass of information, so much of whic
irrelevant to the subject. There are secti
on undescended testes, varicocele, diab
insipidus (3 pages listing 38 caus
inappropriate secretion of antidiur
hormone (2½ pages), hypercalcae
(1½ pages), dysfunctional uterine bleed
and curettage, breast enlargement (4 pa
with 97 causes), and the treatment
leukaemia; while it lacks precision
detail where precise instructions
needed and where differential diagn
is important. For instance, in the sec
on abdominal pain, the recur
abdominal pain of schoolchildren is
mentioned: in the section on for
bodies in the oesophagus, there is
mention of when removal of the objec
advised: in sections on appendi
(p. 12) and intussusception (p. 395) t

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o discussion of the vitally important iations from the classical picture and refore of the difficulties in diagnosis; clinical picture of appendicitis in ncy is not mentioned.

he book lacks balance: in numerous tions the common and important ditions in differential diagnosis are er not mentioned, or are mentioned y at the end of the section: faeces ows hydrops of the gall bladder or chal cyst as a cause of abdominal sses. There are sections on traumatic mobilia, acute prostatitis, and the ifying epithelioma of Malherbe, cribed as a 'fairly common disease'. re is a list of 64 causes of hypoglymia, including nesidioblastosis, but the oglycaemic troubles of the diabetic are mentioned. It is remarkable that reas at least 90% of childhood ptoms may be the side effects of drugs se are scarcely ever mentioned in erential diagnosis.

cannot recommend this book.

CYNTHIA M. ILLINGWORTH

Shorter notices

Increased Intracranial Pressure in Children. Diagnosis and Treatment. Major Problems in Clinical Paediatrics, Volume 8. By W. E. Bell and W. F. McCormick. (Pp. 485; illustrated + tables. £21.00 hardback.) Holt-Saunders: Eastbourne. 1978.

Elegantly produced, like all the volumes in this series, and well illustrated. Straightforward accounts of hydrocephalus, tumours, etc. Disappointingly vague on some difficult areas like the diagnosis of cerebral oedema, and whether to do a lumbar puncture in the child with suspected increased pressure.

Pediatric Neurology and Neurosurgery. Edited by R. A. Thompson and J. R. Green. (Pp. 420; illustrated + tables. £17.50 hardback.) SP Medical and Scientific: London. 1978.

Not a textbook, but a collection of reviews of some problems in this field including prenatal diagnosis, migrainous syndrome, some aspects of convulsions including surgery for epilepsy, and rather selective brief chapters on neurosurgery of trauma and tumours. Nothing very new, and no clear indication of the intended audience.

Practical Paediatric Endocrinology. By C. G. D. Brook. (Pp. 142; illustrated + tables. £6.30.) Academic Press: London. 1978.

Although it may be difficult to see who is going to find this 'slim volume' of 129 pages just what they need, those who do read it will discover that the author's potted experience does often provide in a few simple sentences what a larger textbook takes a few pages and much circumlocution to say. At a time when medical texts tend to be painfully overblown, telling the reader more than he wants to know and at far greater length, it is something of a pleasure to find one which tells him, if anything, rather less that he would like.

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Referees 1978

We continue to depend heavily on the essential help we get from our referees who assess and, in many cases, suggest significant improvements to the papers. This is the only opportunity the Editors have to acknowledge the work done by them during the past year.

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SENSORY-MOTOR DYSFUNCTION AND THERAPY IN INFANCY AND EARLY CHILDHOOD *by* **Delmont Morrison** *and* **Patricia C. Pothier,** *both of Univ. of California, San Francisco, California; and* **Katy Horr,** *Miller West Development Center, San Pablo, California.* The theory of and research into sensory-motor therapy with infants and young children, assessment and therapeutic techniques used with these children, and the relationship between sensory-motor and emotional development are discussed. Specific topics include intervention, motor development and dysfunction, habilitation and remediation, and interventions for early occurring emotional disturbances. *'78, 288 pp., 67 il., 2 tables, $14.75*

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Archives of Disease in Childhood, 1979, **54**, 249–262

Review article

Recognition and management of children with increased lead absorption

J. JULIAN CHISOLM, JR AND DONALD BARLTROP

Baltimore City Hospital, USA, and Westminster Medical School, London

Childhood lead poisoning has been increasingly recognised in the USA where large-scale screening programmes detect some 40 000 cases of undue lead absorption a year. This contrasts with data from the UK where about 100 cases are recognised each year. The situation in other countries is largely unknown, although small surveys have revealed cases from a wide variety of sources. These apparent discrepancies probably reflect differences in clinical awareness, the availability of practical screening tests, and differences in the definition of acceptable degrees of exposure.

Within the last few years practical and effective screening tests for the early detection of undue lead absorption have been developed, but these have not been generally introduced. They include the determination of lead and erythrocyte protoporphyrin (FEP) in microlitre samples of blood. These tests have provided evidence of undue lead absorption from previously unrecognised sources. Thus, dusts contaminated with lead derived from atmospheric deposition, industrial clothing, and degradation of paint films, have now been shown to be important contributory factors. Many children thus affected are asymptomatic, and classical childhood plumbism and encephalopathy at present are rare.

The identification of asymptomatic children has as its objective the institution of effective management in order to prevent serious poisoning and its consequences, and to diminish the potential risks of prolonged low level overexposure. While these risks have not been conclusively demonstrated, it has nevertheless been suggested that subtle neural and behavioural impairments may occur. Moreover, the existence of some children in the population with FEP values that are abnormally high due to lead is no longer considered acceptable.

Sources

Lead is an ubiquitous element with numerous industrial and domestic applications. Children are invariably exposed to lead in general environmental sources—such as food, water, air, dust, and soil—but they may also be exposed to specific and unusual sources including lead paint, lead fishing, curtain, and other weights ingested and retained in the stomach, or the fumes and dust generated by burning lead battery casings, or wood painted with lead pigment paint. Clinical lead poisoning usually occurs as a result of exposure to the second category of items.

General environmental sources. Each major component of the environment—food, water, air, dust, and soil—contributes to the child's total daily intake of lead. Although exposure to lead from these sources is negligible under ordinary circumstances, reports of excess environmental contamination from them are becoming more common. Table 1 lists lead contents for these sources, both under ordinary circumstances and under circumstances of excess environmental contamination.

Food is the principal source of lead for most children. Ordinary daily diets of infants and children may vary widely in lead content; however, limited data suggest that normal diets are associated with average blood lead (PbB) values of 20 μg/100 ml (0·97 μmol/l) whole blood or less (National Academy of Sciences/National Research Council, 1976). More important is the question of contamination of food and drink with exogenous lead. Contamination may occur at the point of origin, during processing, or during preparation and serving at home. Sources of contamination at the point of origin include lead

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Table 1 *Sources of lead in a child's environment*

- Food
  - Mixed diet (range of means 53–132 μg/day).[1,2] Mean 9·43 μg/kg per day[3]
  - Bottled baby foods (mean 35 μg/l)[4]
  - Human milk 6–59 μg/l[5]
  - *Contaminated sources*
    - Tinned baby foods mean 202 μg/l[4]
    - Cola drink in glazed pottery mug 2000 μg/l[6]
    - Bone meal (health food) 60–190 μg/g[7]
- Water
  - Standards: WHO <100 μg/l[8]
    PHS (USA) <50 μg/l[8]
  - *Contaminated sources*
    - Up to 1850 μg/l[9]
    - 2595 samples[8] 1·4%>50 μg/l, maximum 640 μg/l
- Air
  - Usual lead content 1–2 μg/m³
  - *Contaminated sources*
    - Smelter A[10] ≳ 1·6 km, 8–10 μg/m³
    - Smelter B[11] ≳ 4·0 km, 14–16 μg/m³
- Soil
  - Remote areas 2–200 μg/g[12]
  - *Contaminated sources*
    - Within 1·6 km of smelter B[11] geometric mean ≃ 7600 μg/g
    - Urban residential[13] 9–7890 (median 585) μg/g
    - Garden soil (old mining area)[14] geometric mean 1028 μg/g
    - City parks 194–3357 μg/g[12]
- House dust
  - New inner city homes 2–24 μg/ft² floor surface[15]
  - *Contaminated sources*
    - Old inner city homes 33–486 μg/ft² floor surface[15]
    - Mean 11 000 μg/g[16], suburban 300 μg/g[17], urban 750 μg/g[17]
    - Homes of lead smelter workers: geometric mean 2687 μg/g[18]
    - Homes near smelter A[10] < 1·6 km geometric mean = 22 191 μg/g
      1·7–3·2 km geometric mean 2124 μg/g

[1] Barltrop and Strehlow, 1978; [2] Barltrop and Killala, 1967; [3] Ziegler *et al.*, 1978; [4] Mitchell and Aldous, 1974; [5] Dillon *et al.*, 1974; [6] Harris and Elsea, 1967; [7] Crosby, 1977; [8] National Academy of Sciences/National Research Council, 1977; [9] Beattie *et al.*, 1972; [10] Landrigan *et al.*, 1975; [11] Yankel *et al.*, 1977; [12] National Academy of Sciences Committee on Biologic Effects of Atmospheric Pollutants, 1972; [13] Galke *et al.*, 1975; [14] Barltrop *et al.*, 1975; [15] Vostal *et al.*, 1974; [16] Lepow *et al.*, 1974; [17] Creason *et al.*, 1975; [18] Baker *et al.*, 1977.

arsenate insecticides used on fruit trees, fertiliser made from sewage sludge, and exhaust fumes from cars and lorries from roads adjacent to gardens in which leafy green vegetables such as lettuces are grown. Even so, contamination by the use of lead solder to seal tins is more important. Mitchell and Aldous (1974) found upon examination of 256 tins that the contents of 62% contained Pb>100 μg/l, 37% contained >200 μg/l, and 12% contained >400 μg/l. In similar foods in glass or aluminium containers, only 1% had lead levels >200 μg/l. Much more serious is the cooking and serving of food in ancient pewter or imperfectly glazed ceramic utensils. Milligram quantities of lead can be leached from such vessels, especially by acidic items (e.g. fruits, fruit juices, tomatoes, cider, wine, cola drinks, and soda). Fatal and nonfatal cases of encephalopathy in young children have been traced to the consumption of beverages from improperly lead-glazed vessels (Klein *et al.*, 1970; Sitarz, 1975). Severe lead poisoning in 2 infants was traced to electric kettles with lead-soldered heating coils used to boil water for the infants' formulae (Ng and Martin, 1977; Wigle and Charlebois, 1978). Human milk is reported to contain Pb 6–59 μg/l (Dillon *et al.*, 1974). As lead is secreted in human milk, a nursing mother with increased lead absorption would be expected to produce milk with increased lead content. Lead poisoning has also been reported in people using bone meal as a dietary supplement (Crosby, 1977) and Chinese herbal medicines (Lightfoote *et al.*, 1977).

Drinking water ordinarily contains only traces of lead; however, it may be contaminated if plumbosolvent soft waters of low pH are conveyed in lead pipes (National Academy of Sciences/National Research Council, 1977). Water collected at the tap serviced by 969 public water systems in the USA had an average lead content of 13·1 μg/l and only 1·4% of 2595 samples contained more lead than the drinking water standard set by the US Public Health Service 1962 of 50 μg/l (McCabe *et al.*, 1970). In the UK where soft water is more common, drinking water from approximately 1·7 million household exceeds the WHO limit of Pb 100 μg/l on the first flush sample. Values as high as 1800 μg/l have been reported (Beattie *et al.*, 1972). Similar, but not as severe, contamination of drinking water has been reported in the north eastern USA (National Academy of Sciences/National Research Council, 1977).

The contribution of atmospheric lead to daily intake has been the subject of controversy. Urban air generally contains 1 to 2 μg respirable lead/m³ derived from numerous sources, including exhaust fumes from cars, industrial emissions, and the burning of fossil fuels (World Health Organisation, 1977). Pronounced local variations may occur in relation to stationary sources such as lead smelters (Table 1). Wide variations may also occur seasonally or because of thermal inversions. In London, for example, atmospheric lead concentrations near a road increased during the winter when thermal inversions are most common (D. Barltrop and C. D. Strehlow, unpublished data). For adults, it has been calculated that PbB will increase by 2 μg/100ml (0·097 μmol/l) for each 1 μg/m³ in air (Chamberlain *et al.*, 1978), but it is not yet known whether these values are directly applicable to children. Williams *et al.* (1933) traced an outbreak of severe lead poisoning to the burning of discarded battery casings in the home. More recently, symptomatic lead poisoning was reported in people burning, sanding, and scraping old lead while renovating old homes (Wolf, 1973; Feldman, 1978). Burning of newspaper 'logs' in domestic fireplaces was associated with increased lead absorption in an infant (Perkins and Oski, 1976).

Household dust and soils can be contaminated by the powdering and flaking of old lead paint (Vostal *et al.*, 1974), fallout from atmospheric pollution (Yankel *et al.*, 1977), or by lead-bearing dust being carried into the home on the clothing of workers employed in the lead trades (Baker *et al.*, 1977). The relative contribution to the total lead content of household dust from each of these sources is exceedingly difficult to determine (Bridbord, 1977). In one study in an urban area, Galke *et al.* (1975) found that PbB in children was related to soil lead which, in turn, was related to both automotive traffic density and leaded house paint. Table 2 shows the relationship between dust lead and blood lead level in 38 children aged between one and 6 years. This and other studies indicate that there is a significant correlation between household dust containing <1000–1500 ppm lead and PbB >40 μg (>1·93 μmol) in children. Domestic garden soils may also contain significant amounts of lead. Higher concentrations are generally found within a few metres of the house as a result of decomposition of external painted surfaces (ter Haar and Aronow, 1974; Galke *et al.*, 1975). An increase in the geometric mean blood lead concentration of young children of approximately 8 μg/100 ml (0·4 μmol/l) was found in a district in which the mean soil lead concentration exceeded 10 000 ppm compared with a control district in which the soil lead content was <1000 ppm (Barltrop *et al.*, 1975).

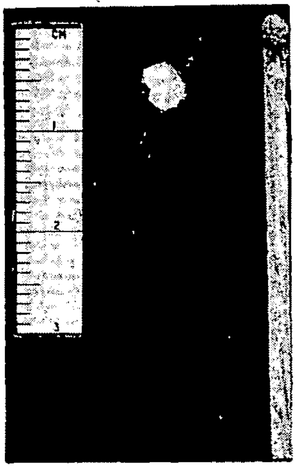

Fig. 1 *Paint flake weighing 10 mg containing 10% lead (1000 μg). Match and cm scale for comparison.*

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Specific and unusual high dose sources. The ingestion of lead-based household paint is without doubt the main source of serious paediatric lead poisoning (National Academy of Sciences Committee on Biologic Effects of Atmospheric Pollutants, 1972; National Academy of Sciences/National Research Council, 1976). Such paints may contain 1–70% lead, so that tiny flakes contain a highly toxic dose (Fig. 1). Lead poisoning is most prevalent in old poorly-maintained houses in which there is flaking paint, and in families in which young children lack proper supervision. Sporadic cases also occur due to the ingestion of lead fishing weights, lead curtain weights, or lead shot (Seto and Freeman, 1964). Less common sources include jewellery painted with lead to simulate pearl, inhalation of fumes of leaded gasoline (Boeckx *et al.*, 1977), cosmetics (Warley *et al.*, 1968), decals* on cocktail glasses (Natelson and Fred, 1976), and hobbies that use ceramics or leaded stained glass. Although tetraethyl lead poisoning caused by sniffing gasoline is more common in teenagers, cases have also been reported in children under 12.

Table 2 *Comparison of lead in household dust with blood lead in children of lead workers**

No. of children	*Children's blood lead* (μg/100 *ml* ± *SD*)	*Dust lead concentration* (*ppm*)
18	21·8 ± 7·8	0–1000
5	41·6† ± 11·1	1000–2000
5	46·2† ± 21·1	2000–3000
4	65·0† ± 10·4	5000–6000
6	73·3† ± 34·0	7000–80 000

*Employed in secondary lead smelter.

†Significantly > mean level than in children exposed to 0–1000 ppm level of lead in dust (P<0·001).

Adapted from Baker *et al.* (1977).

Conversion: traditional units to SI—blood lead: 1 μg/100 ml ≈ 0·048 μmol/l.

Metabolism and effects

Metabolism. Among people with no unusual lead exposure, the total body lead burden may increase from 0·2 mg at birth to >200 mg during life; however, the increase is limited almost entirely to increasing storage of lead in bone. The concentration of lead in soft tissues normally remains low and relatively constant throughout life (Barry, 1975). Lead incorporated into bone is virtually inert, metabolically speaking. The toxic effects of lead are related to increases in its concentration in the soft tissues. Although there are no data on dose-response for ingested lead in children, it is of interest to compare studies by Kehoe (1961) on chronic adult volunteer lead feeding with the information in children (Mahaffey, 1977). Kehoe found that raised levels of PbB to 80 μg (3·9 μmol) and a likelihood of symptomatic poisoning could be induced after 3 or

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*A transfer (picture or design).

4 months with a daily dose of 4 mg Pb. From data on faecal lead, Barltrop and Killala (1967) and Chisolm and Harrison (1956) calculated that the comparable dose in young children is about 1 mg/day—i.e. 25% of the adult dose. These intakes are equivalent on the basis of surface area, and both are about 10 times the normal dietary intake for adults and children. Because lead is slowly metabolised, soft tissue lead concentrations, including PbB, decrease very slowly for months or years after the excessive intake has stopped.

Recent kinetic studies with a stable lead isotope (^{204}Pb) in 5 healthy men suggest a 3-compartmental model for lead metabolism (Rabinowitz *et al.*, 1976). The 2 smaller compartments, one of which is related to excretion of lead via urine and the other to excretion via other routes, consist of blood, soft tissues, and probably, a small exchangeable fraction of lead in bone. The mean lives of lead in these compartments are 35 and 40 days. Rabinowitz *et al.* (1976) estimate that the mean life of lead in bone is about 27 years. Comparable long-term data on steady-state kinetics are not available for young children. Multiple 3-day balances in American infants of under 2 years show wide variation in lead intakes from normal infant foods (0·83 to 22·61 µg/kg per day; mean, 9·43 µg/kg per day) (Ziegler *et al.*, 1978). While net retention for all studies averaged 11% of intake, retention increased to 32% when dietary intake exceeded Pb 5 µg/kg per day. Retention of lead also showed a weak inverse correlation with dietary calcium. The retention of lead by children varies and many children in the short term may be in negative lead balance (Barltrop and Strehlow, 1978). A high incidence of suboptimal dietary intake of calcium was reported in children with increased lead absorption (Mahaffey, 1977; Sorrell *et al.*, 1977). A significant decrease in serum 25-hydroxy vitamin D was reported in children with increased lead absorption (Sorrell *et al.*, 1977; Strehlow and Barltrop, 1978). These clinical studies are consistent with studies in animals which indicate that deficient intake of calcium enhances absorption, retention, and toxicity of lead (Barltrop and Khoo, 1975; Barton *et al.*, 1978; Goyer, 1978). Other experimental studies show that deficient dietary intakes of iron, copper, zinc, and selenium, as well as excessive dietary intake of fat, also increase absorption, retention, and toxicity of lead (Chisolm, 1978). Of interest is the observation that dietary iron in excess of requirements in rats may decrease rentention of lead (Mahaffey *et al.*, 1978).

Effects. In man, the principal target organs for lead are the erythroid cells of the bone marrow, the central and peripheral nervous systems, and the kidney. The inhibitory effects of lead on erythropoiesis are reversible; however, severe acute or chronic clinical lead poisoning may be followed by irreversible injury to the nervous system and kidney. Scattered case reports suggest that acute clinical lead poisoning with PbB >100 µg (>4·8 µmol) may also be associated with impaired uptake of iodine by the thyroid, impairment of the renin-aldosterone system, and ECG changes compatible with myocarditis: the effects are apparently reversible (National Academy of Sciences Committee on Biologic Effects of Atmospheric Pollutants, 1972). The varied cellular effects, which are demonstrable experimentally *in vitro*, are beyond the scope of this report, but are reviewed elsewhere (Vallee and Ulmer, 1972; Granick *et al.*, 1978). The classical concepts of toxicology have been adapted to evaluate lead exposure, absorption, and effect in human populations (Nordberg, 1976) and are summarised elsewhere (Chisolm *et al.*, 1975). In experimental toxicology, the concentration of lead and its effects may be measured directly in affected cells and cell components. In human studies, PbB and chelatable lead* are used as indicators of its concentration in the tissues (internal dose), while various metabolites in blood and urine serve as indicators of its effect in the tissues.

Increase in δ-aminolaevulinic acid in urine (ALAU) is one of the biochemical indicators of lead's inhibitory effects on heme synthesis. The curvilinear dose-effect relationship between PbB and ALAU is such that ALAU increases very sharply as PbB rises above 40–50 µg (1·9–2·4 µmol). The rate of increase is so sharp that ALAU may vary from normal to 5 times greater than normal within the rather narrow 50–60 µg (2·4–2·9 µmol) range in PbB (Fig. 2). Similarly, clinical response also varies, as the full clinical spectrum from no symptoms to fatal acute encephalopathy in children may be found within the PbB range of 100–200 µg (4·8–9·7 µmol) (Table 3). Clearly, responses cannot be ascertained from PbB alone.

New definitions of the terms 'critical organ' and 'critical effect' relative to lead have been proposed (Nordberg, 1976) and have important implications for preventive medicine. Derangement of Hb synthesis in the erythroid cells of the bone marrow is now considered the critical or first adverse effect. Current preventive health policies rest on the assumption that intervention on the basis of biochemical evidence of derangement of Hb synthesis will suffice to prevent the more serious and possibly long-term adverse effect of lead in the nervous system and kidney. It should be borne in mind,

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*Chelatable lead = quantity of lead excreted in urine after standardised dose of CaEDTA or D-penicillamine.

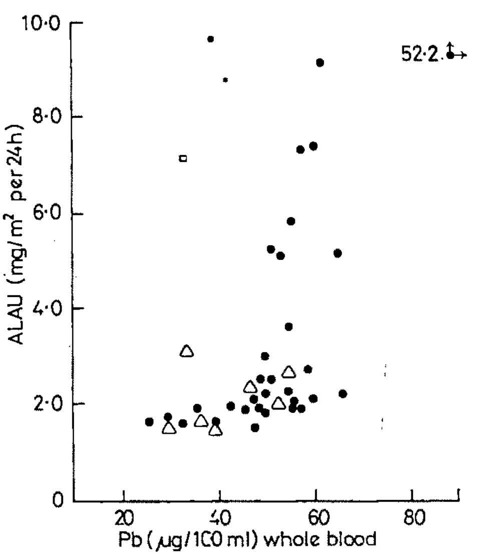

Fig. 2 *Relationship between PbB and ALAU in children. For children with PbB between 8 and 30 µg, normal daily excretion averages 1·1 ± 0·4 mg ALAU/m² per 24 h (upper limit of normal 2·3 mg ALAU/m² per 24 h) (Chisolm et al., 1976). Daily output of ALAU, which is related to surface area in children, increases sharply as PbB increases above 50 µg; however, there are pronounced differences in ALAU among individuals with PbB in the 50–60 µg range. The two anomalous cases shown as □ and △ had sickle cell disease and sickle cell trait, respectively.*

Table 3 *Relationship between blood lead concentration and symptoms of plumbism in children**

Clinical group	*n*	*Blood lead concentration* (µg/*100ml*)	
		Median	*Range*
Acute encephalopathy			
Fatalities	98	295	138–750
Survivors	99	270	88–1,310
Acute plumbism (non-encephalopathic)	40	135	63–450
Increased lead absorption (? clinical symptoms)†	46	85	60–300

*Adapted from National Academy of Sciences Committee on Biologic Effects of Atmospheric Pollutants (1972), as compiled from reports of Chisolm and Harrison (1956), Chisolm (1962, 1968), and Baltimore City Health Department.

†Although some children in this group had nonspecific symptoms compatible with plumbism, they also had other conditions which give rise to the same symptoms, making clinical diagnosis uncertain.

For conversion to SI units see footnote to Table 2.

however, that biochemical indicators of lead's effects on heme synthesis in erythrocytes are extraordinarily sensitive and not entirely specific for lead: FEP is raised in both iron deficiency and increased lead absorption, and δ-aminolaevulinic acid dehydratase (ALAD) is a zinc-dependent enzyme inhibited by lead (Chisolm, 1978).

Heme synthesis in bone marrow

All cells synthesise heme for their own hemoproteins (Hb, myoglobin, catalase, cytochromes, P-450, etc.) via a common metabolic pathway. Experimental data show that lead interferes with this process in all organs so far studied; however, the erythroid cells of the bone marrow are the most sensitive (Moore, 1975; Nordberg, 1976). There are 6 major enzymatic steps in the formation of heme. In lead-poisoned adults, increased activity of δ-aminolaevulinic acid synthetase, partial inhibition of ALAD, coproporphyrinogen oxidase, and ferrochelatase has been demonstrated (Wada *et al.*, 1972; Campbell *et al.*, 1977). These enzymatic changes account for the pattern of metabolites found in blood and urine, which is pathognomonic for lead; namely, decreased *in vitro* activity of ALAD in circulating erythrocytes, increased FEP, increased excretion of ALAU and coproporphyrin (CPU), and normal or nearly normal excretion of porphobilinogen and uroporphyrin in urine. Excess lead also impairs the uptake and use of iron, as well as the synthesis of globin in developing erythrocytes. In children the circulating erythrocytes are hypochromic and microcytic, and reticulocytosis is sometimes found. The morphology of the peripheral blood in children with plumbism is virtually identical with that found in iron deficiency, a condition with which plumbism is often associated. Lead also impairs the activity of 5′-pyrimidine nucleotidase, which accounts for the basophilic stippling of erythrocytes associated with severe and chronic plumbism (Valentine *et al.*, 1976). When PbB >60 µg, Hb and haematocrit are significantly reduced (Rosen *et al.*, 1974; Landrigan *et al.*, 1976). Pueschel *et al.* (1972) and Betts *et al.* (1973) have reported an increasing frequency of reduced Hb when PbB>40 µg. These differences are probably attributable to differences in the prevalence of iron deficiency in the populations of children studied. The PbB threshold for increase in ALAU in children is between 40 and 50 µg Pb. Although the threshold for FEP in children is apparently lower, the increase is generally slight—up to about 30 µg Pb—above which it increases exponentially (Stockman *et al.*, 1975; Hanna *et al.*, 1976; World Health Organisation, 1977). FEP may also be increased in iron-deficient children with PbB<30 µg (<1·5 µmol) (Stockman *et al.*, 1975; Koller *et al.*, 1978; Strehlow and Barltrop, 1978).

Kidney and bone

Clinical lead poisoning may be associated with both acute and chronic effects in the kidney. In children with acute encephalopathy and PbB>150 μg (7·2 μmol), the full Fanconi triad (hyperaminoaciduria, glycosuria, and hyperphosphaturia) in the presence of hypophosphataemia has been reported (Chisolm, 1962). The Fanconi triad is reversible. Children with a history of clinical plumbism during the preschool years in the USA have not shown evidence of residual renal injury in adolescence or early adult life (Tepper, 1963; Chisolm, 1970). This experience differs from that in Australia where an increased frequency of late lead nephropathy was reported (Nye, 1929; Henderson and Inglis, 1957). Emmerson (1968) described the syndrome as characterised by progressive loss of renal function, often with hyperuricaemia and saternine gout, terminating with renal failure. Some of these patients were also mentally retarded and had pes cavus deformity due to old peripheral neuropathy. In the Australian children, symptomatic episodes of plumbism extended well beyond the preschool years, up to 10 to 12 years. It seems likely that prolonged poisoning was an important factor in the irreversible renal injury sustained by the Australian children.

The bands of increased density at the metaphyses of growing long bones characteristic of lead poisoning in children are generally limited to those who have sustained PbB>50 to 60 μg (Betts *et al.*, 1973). Although these *x*-ray changes are generally called 'lead lines', a major factor is distortion of bone architecture and increased mineral deposition caused by lead. Their presence suggests that one of the body's important compensatory mechanisms—storage of excess lead in bone—is being impaired.

Neurological and behavioural effects

Acute lead encephalopathy is the most severe clinical form of lead poisoning. Pathologically, it is characterised by extensive cerebral vasculopathy and massive oedema of the brain (Clasen *et al.*, 1974). It is most common during the summer months in children of under 3. Before the advent of chelating agents, 65% of severe cases terminated fatally. In recent years, chelation treatment with a combination of BAL and CaEDTA has reduced mortality to less than 5% (Coffin *et al.*, 1966; Chisolm, 1968). When chelation treatment is begun *after* the symptoms of acute encephalopathy appear, the incidence of severe permanent sequelae—such as mental retardation, seizure disorders, blindness, and hemiparesis—is estimated at 25 to 50%, even if abnormal re-exposure is promptly stopped (Chisolm and Harrison, 1957; Byers, 1959; Chisolm, 1973). Byers and Lord (1943) reported that 19 of 20 children with at least one symptomatic episode of plumbism subsequently did poorly in school, despite the fact that standard psychometric tests indicated normal intelligence. Failure in school was attributed to behavioural disorders, lack of attention, perseveration, and visual-motor impairment. In a similar group of 425 children, Perlstein and Attala (1966) found that 39% sustained severe neurological sequelae. Although data on PbB are not systematically given, the data in Table 3 suggest that they were describing the chronic course and outcome in children in whom PbB repeatedly exceeded 80 to 100 μg. In the USA, screening data currently reported to the Center for Disease Control indicate that 3 to 20% of preschool children have increased lead absorption, as shown by PbB in the 30 to 80 μg range. Most are asymptomatic, while mild nonspecific symptoms compatible with early plumbism are reported in a few. In children living near primary smelters (Landrigan *et al.*, 1975) or in the homes of workers who carry fine particulate lead home on their clothing (Baker *et al.*, 1977), the proportion of children with increased lead absorption is somewhat higher. Even so, most are asymptomatic. Whether such children are at significant risk for subtle, but significant neurobehavioural impairment has aroused much concern. During the postnatal phase of rapid neurodevelopment, which in children extends from birth to 2 or 3 years, the brain may be especially vulnerable to nutritional and toxic insults (Dobbing and Smart, 1974). Evidence is still incomplete and clinical studies have given conflicting results. Experimentally, lead can be shown *in vitro* to inhibit the calcium-mediated release of neuro-transmitters, cause demyelinisation of the axon, impair oxidative metabolism in the brain, and impede transmission at the neuromuscular junction (Granick *et al.*, 1978). Animals dosed with lead during the phase of rapid postnatal neurodevelopment showed slowed learning (Brown, 1975), maturational delay (Grant *et al.*, 1976), and scotopic defects (Bushnell *et al.*, 1977). During infancy, PbB values in the range of 40 to 80 μg were reached in these experiments, although the deficits were not shown until after PbB levels had returned to normal. Thus, the experimental data suggest that increased lead absorption during the phase of rapid neurodevelopment may induce later neurobehavioural deficits. Some animal studies are confounded by inadequate nutritional controls (Barltrop and Khoo, 1975; Reiter *et al.*, 1975). In view of other experimental studies which indicate that deficiencies of iron and zinc may have similar subtle adverse neurobehavioural effects, resolution of this question still awaits appropriately designed studies.

Clinical studies have also given conflicting results. Lansdown *et al.* (1974) and McNeil *et al.* (1975) did not find deficits at school age, and Kotok *et al.* (1977) attributed the deficits they found to pre-existing factors. Conversely, Albert *et al.* (1974), Rummo (1974), and de la Burdé and Choate (1975) did find deficits at school age which they attributed to lead. The only workers who have conducted a study prospectively from birth to 8 years of age are de la Burdé and Choate (1975), and their findings are similar to those of Byers and Lord (1943), inasmuch as poor performance in school was also attributable primarily to behavioural problems. These various studies suggest that no significant impairment has been found in children from higher socioeconomic classes who were well nourished and who generally had PbB<50 μg. Positive findings have been in children from the lowest socioeconomic class in deteriorated urban areas whose source of lead was paint, and who sustained PbB>50–60 μg, and in whom poor nutritional status was strongly suspected. Neurobehavioural impairment at school age has been related to raised levels of lead in shed deciduous teeth (Needleman *et al.*, 1978); however, these data do not give a retrospective estimate of earlier blood and soft tissue lead levels. David *et al.* (1972) were the first to suggest that asymptomatic increased lead absorption might be one of the aetiological factors in hyperactivity in children. This provocative hypothesis has yet to be tested adequately. Initially, experimental studies in which high doses of lead were used in suckling animals seemed to confirm the hypothesis of David *et al.* (1972); however, subsequent studies with lower doses have generally not resulted in increased locomotor activity (e.g. Reiter *et al.*, 1975).

Peripheral neuropathy is rare in children. Among the 15 cases recently reported from America, 7 were in children with sickle cell disease (Anku and Harris, 1974; Erenberg *et al.*, 1974). This striking clinical observation may be important, inasmuch as sickle cell disease is apparently associated with secondary zinc deficiency (Prasad *et al.*, 1975), and studies in animals indicate that zinc is protective against lead.

Management

Clinical management. Paediatric intervention should be started in the presymptomatic phase in order to lessen the risk of serious injury to the nervous system. Indeed, most referrals today are likely to be asymptomatic children who have been identified in screening programmes, epidemiological surveys, or as housemates of an index case of poisoning. The nature of the exposure (see Environmental management), as well as the age of the child and his nutritional, genetic, developmental, psychosocial, and behavioural status should be weighed in making a plan of management tailored to his needs. Children under 3, in whom pica is common (Barltrop, 1966), and in whom the rapid postnatal phase of neurodevelopment is not yet complete, usually need closer follow-up than older children. Adequate dietary intakes, particularly of calcium, iron, and zinc must be assured, while excessive dietary fat is to be avoided. Response to medicinal iron, which is often required, can be monitored by serial FEP tests (Fig. 3).

For those who are intolerant of milk, 'lactose-free' milk products, or an alternative source, will be necessary to ensure an adequate calcium intake. Clinical experience and the occurrence of zinc deficiency suggest that those with a sickling disease (Hb SS, SC, or S-thal) have a higher susceptibility to lead and so should receive priority for transfer to a 'low-lead' environment. Mentally retarded children, in whom chronic pica is prevalent, should receive PbB and FEP tests periodically as part of their regular health care, even if initial tests give normal results.

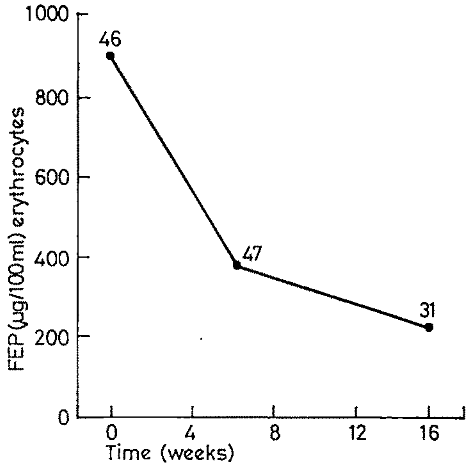

Fig. 3 *Combined influence of iron deficiency and increased lead absorption on erythrocyte protoporphyrin (FEP). Line connecting points shows trend in FEP, while numbers adjacent to points show PbB values. Clinical history and additional data (serum FE = 21 μg/100 ml; (3·76 μmol/l); TIBC = 544 μg (97·14 μmol/l); % saturation = 3·9%) indicated deficient dietary intake of iron and residence in a dilapidated old house. During the first 7 weeks of treatment with iron, FEP decreased from 900 to 400 μg/100 ml erythrocytes, and haematocrit increased substantially, although PbB remained unchanged. The family then moved from an old house to public housing in Baltimore, USA, where the use of lead-containing paints has been prohibited for the last 40 years. Iron treatment was continued and both PbB and FEP decreased further.*

The term pica refers to the magpie, a bird of both capricious and voracious appetite. The habit of pica may be defined as the repetitive search for and ingestion of nonedible items. In children, it starts at about 12 months and occurs in about half of one- to 3-year-old children (Barltrop, 1966). Its aetiology is not understood. Lourie *et al.* (1963) considered pica an important symptom of familial stress and disorganisation, with resultant lack of mothering. Success in ameliorating a child's pica often depends on the degree to which such family problems can be resolved.

In heavily contaminated areas, periodic testing throughout the preschool years is indicated. A child with increased lead absorption should be checked every 3 months for at least a year until PbB and FEP steadily decrease and stabilise at or near the normal range, indicating satisfactory abatement of hazards and probable diminution of pica. Sometimes initial clinical evaluation may suggest the need for follow-up, even if the initial PbB levels are normal, as an infant with pica may subsequently gain access to a hazardous lead source (Fig. 4). Reigart and Whitlock (1976) found that a raised level of FEP, together with normal or minor increase in PbB is often predictive in young children of subsequent increase in PbB to potentially hazardous levels. The renovation of old leaded dwellings is hazardous not only for workmen (Feldman, 1978), but especially for young children who can experience a sharp rise in lead absorption (Fig. 5), even to symptomatic levels. Young children and pregnant women should seek residence elsewhere—night and day—until renovation is complete and the debris removed from the premises, an admonition not always heeded. The data in Fig. 5 illustrate another common occurrence; incomplete abatement of residential lead hazards with a spike in PbB in the child on return home.

While removal of lead from the child's environment is the key to successful clinical management, selective use of chelating agents can be a valuable adjunct. Three agents are used: edathamil calcium disodium (CaEDTA), 2, 3-dimercapto-1-propanol (BAL), and D-penicillamine (PCA). According to principles described elsewhere (Chisolm, 1968), the greater the physician's estimate of soft tissue lead

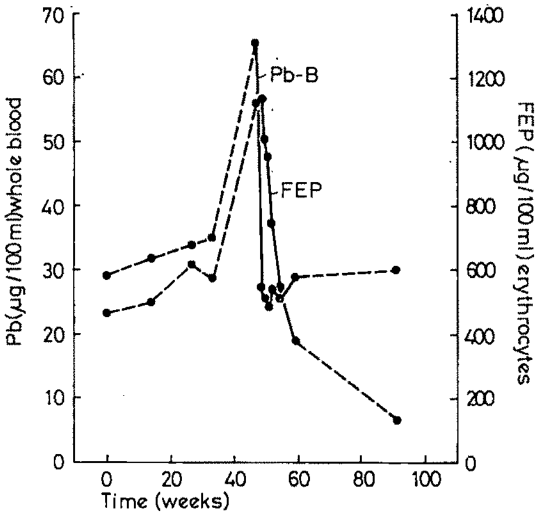

Fig. 4 *PbB and FEP in an iron-deficient infant with indiscriminant pica.*
Initial data showed residence in safe housing, normal lead absorption, and iron deficiency in a 12-month-old infant; however, a positive history of pica, visits to relatives in poor housing, and a working mother indicated the need for prolonged follow-up. Sharp rise in PbB and FEP coincided with relegation of the infant's care to young irresponsible relatives during the summer. Patient was treated (solid portion of line) in hospital with chelating agents, dietary correction, medicinal iron, behavioural management to lessen pica, and return to safe housing area.

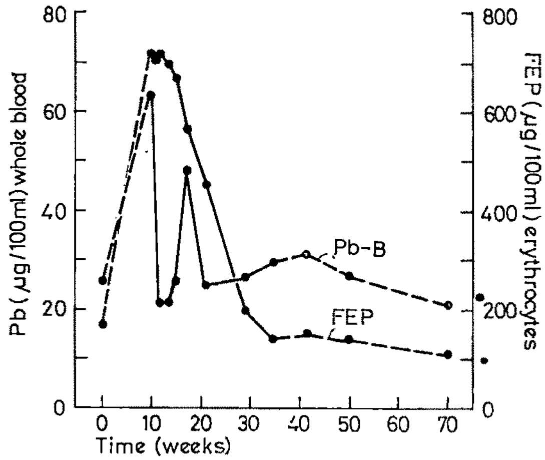

Fig 5 *PbB and FEP changes in an infant during deleading of an old home.*
The infant remained in the home during burning, scraping, and sanding of old lead-bearing paint. Both PbB and FEP levels increased dramatically during a fortnight of intense exposure. The infant was placed in hospital and treated with chelating agents, medicinal iron, and prophylactic amounts of copper and zinc. A rise in PbB from 22 to 47 µg (1·06 to 2·3 µmol) during fortnight immediately after discharge indicated incomplete hazard abatement. Family thereupon moved to modern 'lead-free' public housing. PbB decreased promptly, while FEP continued to decrease.

concentrations, the higher the initial dosage of chelating agents should be. Conversely, because of the curvilinear relationship between PbB and chelatable lead, *arithmetic* decreases in PbB are associated with *exponential* decreases in the amount of lead mobilised and excreted in the urine (Chisolm *et al.*, 1976). It follows that their use in children with slightly increased soft tissue lead concentrations may be of such limited benefit as to be outweighed by the fact that these agents also remove substantial amounts of zinc and other trace metals which are protective against the toxicity of lead. Parenteral CaEDTA and BAL are considered primary drugs, while oral PCA serves well as a secondary sustaining agent if long-term treatment appears warranted and a low lead environment can be found for the child. Under no circumstances should chelating agents be given while excess lead intake continues. Patients on PCA must be closely monitored for renal (nephrotic syndrome) and haematological reactions (especially neutropenia). CaEDTA is a nonmetabolisable drug which is excreted exclusively by glomerular filtration. Fatal reactions have occurred when its use is continued in anuric patients. CaEDTA and PCA should not be used in asymptomatic or mildly symptomatic patients with intercurrent renal disease. BAL is contraindicated in patients with acute hepatocellular injury and in males with G6PD deficiency. These and other precautions are described more fully elsewhere (Chisolm, 1968; United States Public Health Service, 1978). Details of drug dosage and the treatment of acute encephalopathy are given in the Appendix.

The use of chelation treatment in asymptomatic or questionably symptomatic children with increased lead absorption is controversial, particularly the long-term oral use of PCA. The retrospective study of Albert *et al.* (1974) suggests that chelating agents in such cases may reduce the prevalence and severity of the neurobehavioural sequelae of early childhood plumbism. For children with PbB in the 30–50 μg range, correction of nutritional deficits and steps to reduce exposure, including stringent dust control in the home, should suffice. A disproportionate increase in FEP (Fig. 3) is suggestive of concurrent iron deficiency which should be corrected. An overview of current experimental data and studies on humans suggests that the combination of PbB >50–60 μg and FEP >300 μg/100 ml erythrocytes in a child under 2, and >500 μg/100 ml (8·90/μmol/l) erythrocytes in a child over 2, probably constitute reasonable clinical indications for at least brief courses of chelation treatment. The indication is further strengthened if long-bone *x*-rays are positive for 'lead lines'. The unresolved question is whether or not PbB concentrations sustained >50–60 μg over a period of months or years, even in the absence of continued abnormal ingestion, carries a significant risk for CNS injury.

Lead poisoning and increased lead absorption must be treated as chronic disorders. Often, the doctor, environmental hygienist, public health nurse, and medical-social service personnel have to work as a team. In certain areas of the USA, lead poisoning is a reportable disorder. Children surviving encephalopathy may require long-term management for seizure disorders, gross behavioural aberrations, and special school placement. For children who must perforce live in substandard housing, adequate nutrition may improve their resistance to lead. The effectiveness of any tentative long-term management is best judged by the child's biological response. Satisfactory control of emissions from stationary sources will be followed by decreases in PbB in the nearby population (Yankel *et al.*, 1977).

Environmental management. The objectives of environmental management after the discovery of a case of excessive exposure to lead are twofold: (1) the prevention of re-exposure of the child and (2) the protection of other individuals who may be currently or subsequently exposed. This means that the identified source must be removed or at least measures taken to render it unavailable to young children.

Domestic sources

The most common sources in the home are accessible painted surfaces. The ideal solution is the complete removal of all lead-containing paint accessible to children and its replacement by an appropriate low-lead paint (lead-free) intended for interior use. Although legal provisions to enforce such action are available in some parts of the USA, this is not universal. Much depends on the ownership of the home, the attitude of local housing authorities, and the socioeconomic status of the family. Substantial amounts of fine particulate lead may be released during the course of remedial work, and these may be sufficient to cause significant additional burdens for children who remain resident in the home during renovations (Fig. 5). It is important that all pre-existing paintwork be removed, and that the house is not merely redecorated with an additional layer of paint. Other temporary measures may include accessible painted surfaces being covered with an adhesive plastic material (United States Public Health Service, 1978).

Other domestic sources including glazed ceramics, toys, and surma*, (Table 1) should be controllable by simple advice and removal. Similarly, industrial clothing contaminated with lead should never enter the home, although this may be difficult to enforce. The lead hazard of some industrial processes is not always appreciated (Gafafer, 1966). If heavy contamination of clothing occurs, the only solution is to ensure that the worker has the opportunity of bathing and changes his shoes and clothing at the workplace at the end of each shift. In addition, facilities for the laundering of industrial clothing must be available at the place of work, rather than in the home. Domestic sources of lead may result in heavy contamination of household dust on the floor and in the upholstery of furniture. If this has occurred, then as complete removal as possible of dust should be undertaken, using a vacuum-operated device.

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*Cosmetic used by Asians which sometimes contains lead sulphide.

Contaminated drinking water is usually the consequence of lead plumbing or storage tanks in an area where the water has a high degree of plumbosolvency. The only immediate solution is to provide an alternative supply from a less hazardous source, although the exposure may be mitigated by merely flushing the system for several minutes before use. This is particularly important after prolonged periods in which the water has been static in the delivery system, for example, in the early morning. The only ultimate solution is the removal of lead from the delivery system. While this may be possible for an individual family with a localised source, for example, an improperly soldered joint in a copper pipe or an imperfectly manufactured electric kettle, it may not be immediately applicable if the use of lead in the delivery system is extensive. Thus, in the UK, it has been estimated that the cost of meeting the WHO 'European' standard of 100 μg/l would be of the order of £1000 million. In this context, it should be noted that in the US, a water standard of 25 μg/l has been suggested (National Academy of Sciences/National Research Council, 1977). From a prophylactic standpoint, effective measures may require action at a national rather than a local level. Such measures may include introducing regulations governing the import, manufacture, or sale of lead-based cosmetics, toys, ceramic ware, paint, and graphic materials liable to be used by children at home or in educational establishments. There is little international agreement concerning such regulations. In the USA, the lead content of paints for domestic use has been severely restricted and a regulation restricting this to 0·06% has been promulgated, whereas in the UK a value of 1·0% is still permitted (0·5% for toys and nursery furniture).

Nondomestic sources

Problems arising outside the home are only likely to be found in relation to industrial activities either current or defunct. This may result from direct access to tips or mine tailings of high lead content or dispersion of lead-contaminated dusts from their surface. In addition, lead may be dispersed in the atmosphere as respirable particulate material, the impact of which will depend on local topography and climatic conditions. In such cases, whole communities rather than individuals are likely to be affected and the solutions require the collaboration of several agencies. It is often difficult to identify the routes of transmission of lead in such circumstances or indeed to assess their relative significance. Immediate measures should depend on the severity of the cases. In the event of exposures of sufficient degree to result in frank plumbism, the only ethical choices are either the evacuation of the community or the immediate cessation of emissions. Ideally, atmospheric dispersion from many industrial sources can be substantially diminished by the introduction of effective baghouse (filtration) equipment. Re-entrainment of lead by wind dispersion from unprotected tips and mine tailings can be checked by either removal or covering with an uncontaminated layer of earth. Such sources should be rendered inaccessible to children. The management of contaminated soils and dusts in houses and villages adjacent to industrial sources is not generally amenable to simple measures. Paving with impervious material is expensive and aesthetically unsatisfactory. Treatment of earth surfaces with a resin or similar material in order to diminish wind dispersion may be temporarily effective, but cannot be applied to land used for the cultivation of crops. Frequently, the only solution is the physical removal and replacement of soil in the heavily contaminated inhabited area. However, there are as yet no generally agreed standards for the permissible lead content of surface soils in relation to dwellings or for other uses. Similar considerations apply to the permissible content of respirable lead in the atmosphere. It has been calculated that each 1 μg/m^3 lead contributes approximately 1–2 μg/100 ml to the content of lead in blood. There are as yet no generally agreed air quality standards, although values in the range 1–5 μg/m^3 have been suggested. In the EEC countries a standard of 2 μg/m^3 for residential areas remote from motorways and industry has been recommended, while the US Environmental Protection Agency has advocated 1·5 μg/m^3 of air. It should be noted, however, that such standards are usually intended to apply to mean monthly or even annual values and that transient or seasonal fluctuations may occur.

Conclusions

There is no longer any reasonable doubt that acute lead encephalopathy and recurrent symptomatic plumbism in children can, in a high proportion of cases, result in severe residual CNS injury, including seizure, mental retardation, severely handicapping behavioural disorders and, in rare cases, blindness, and hemiparesis. In asymptomatic or mildly symptomatic plumbism, clinical studies have given conflicting results. There is some evidence, however, that a sustained PbB >50–60 μg/100 ml during early childhood carries a significant risk of subtle neurobehavioural impairment, but not for the more serious sequelae associated with symptomatic lead poisoning. Such subtle deficits do not become evident until later in childhood. Data on immature animals also indicate that subtle cognitive and visual deficits, but not hyperactivity, may result when PbB is sustained in the 50–100 μg range. The effects of unsustained increases of PbB in the same range are unknown. Concurrent marginal or frank nutritional deficiencies especially of iron, calcium, and zinc, as well as the habitual overuse of fat in the diet, may be important cofactors in determining the final clinical outcome. A thorough history to identify all potential sources of overexposure to lead in the child's environment, followed by identification of the actual sources is essential. Separation of the child from sources of lead constitutes the cornerstone of any therapeutic plan. Although the use of combined chelation treatment in acute lead encephalopathy can be life-saving, treatment started *after* the onset of severe symptoms will not prevent the occurrence of CNS sequelae in survivors. Modern screening tests permit the detection of plumbism before the onset of symptoms. The indications for the use of chelating agents in asymptomatic increased lead absorption are uncertain. Emphasis is placed on the need for individual management and long-term follow-up to determine the trends in each child's course. Pica, the response to assimilated lead, and the pattern of neurodevelopment during the first 3–4 years of postnatal life, may make the young child more vulnerable to overexposure to lead than older children and adults.

Appendix: treatment of acute plumbism

In acute lead encephalopathy, treatment with combined BAL-CaEDTA in the following dosage is recommended: BAL, 500 mg/m^2 per 24 h; CaEDTA, 1500 mg/m^2 per 24 h. To lessen pain, procaine is added to the 20% CaEDTA concentrate in a final concentration of 0·5%. Each drug is given by deep IM injection at separate sites simultaneously in divided doses 4-hourly for 5 days. This is maximum dosage. It is unsafe to continue it beyond 5 days. In asymptomatic or very mildly symptomatic patients with confirmed PbB in excess of 80 to 100 μg, the above regimen may be modified as follows: discontinue BAL when used after 48 hours but continue CaEDTA for an additional 48 to 72 hours in reduced dosage of 1000 mg/m^2 per day divided into two or three doses at 8- to 12-hour intervals. If CaEDTA is used alone in patients with initial PbB <80 to 100 μg, 500 mg/m^2 12-hourly either by deep IM injection or by continuous IV infusion for 3 to 5 days should suffice. Patients receiving BAL should be placed on parenteral fluids or clear liquids orally to minimise the vomiting which BAL often causes. Brief courses of chelation treatment are virtually always associated with rebound in PbB, presumably as a result of internal redistribution of lead (Fig. 6). When it is considered desirable to lessen this rebound and maintain soft tissue lead at a low level until the excess lead has been either excreted or well sequestered in bone, an initial course of CaEDTA, with or without BAL, may be followed by oral PCA. Oral PCA should be continued until FEP decreases to near normal. Even so, such patients must still be checked for delayed rebound in PbB and FEP. Although clinical studies are not available, experimental data strongly suggest that prophylactic amounts of iron, zinc, and copper should be given during long-term treatment with PCA to prevent depletion of these metals. Oral dosage of PCA

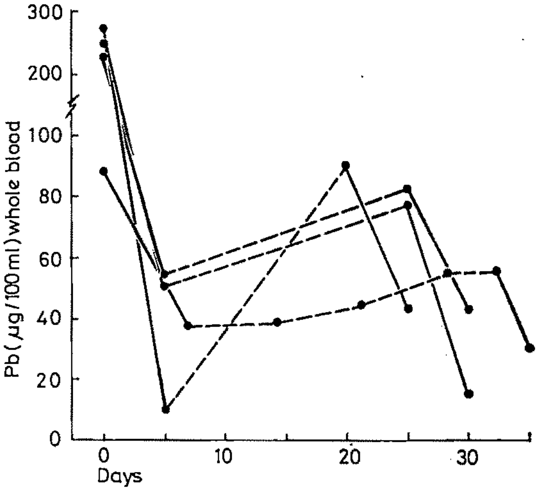

Fig. 6 *Rebound in PbB between brief courses of chelation treatments.*
These data were obtained in 4 children continuously in hospital for 30 to 40 days. The solid bars show the decrease in PbB during 5-day courses of CaEDTA (or BAL-CaEDTA), while the broken lines show the upward trend in PbB between courses of chelating agents. Serial measurements of ALAD, ALAU, and CPU, but not FEP, show virtually identical trends.

should not exceed 600 mg/m^2 per day, given on an empty stomach in chilled fruit juice, if necessary, 2 hours before breakfast.

The use of combined BAL-CaEDTA treatment for acute lead encephalopathy is described in detail elsewhere (Chisolm, 1968). The salient points are: (1) appropriate supportive therapy is just as vital to survival as chelating agents, (2) BAL-CaEDTA therapy must be instituted *promptly*, (3) parenteral fluids are restricted to basal requirements and a minimal estimate of replacement of deficits caused by dehydration, protracted vomiting, or concurrent renal injury due to lead. Adequate, but not excessive urine flow must be established before CaEDTA can be given. Mannitol may be necessary to re-establish adequate urine flow. Initial control of seizures is perhaps best achieved by diazepam, while further convulsive activity should be controlled with paraldehyde until the patient is substantially improved, after which long-term anticonvulsant treatment with phenylhydantoin may be instituted.

Surgical decompression and hypertonic solutions to relieve intracranial pressure and reduce cerebral oedema are contraindicated. Time should not be wasted in attempts to evacuate residual lead from the bowel by enema. Such attempts are futile and the attendant delay jeopardises the child's life. In symptomatic children who do not have obvious evidence of increased intracranial pressure, it is judicious to treat them in hospital as possible incipient cases of encephalopathy and so monitor parenteral fluids and urine output and restrict oral intake during the initial 24 to 48 hours of treatment.

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Annotations

Red cell aplasia in children

Red cell aplasia in children is a condition characterised by failure of erythropoiesis, with normal production of white blood cells and platelets. The disorder is either acquired or constitutional (congenital or inherited). The constitutional disorder is usually permanent, while the acquired variety is often transient, and thereby differs from adult pure red cell aplasia. As the treatment and prognosis of a child with anaemia depend on the diagnosis, the distinctive feature of each disorder is described.

Constitutional red cell aplasia: Diamond-Blackfan anaemia

Children with anaemia without pancytopenia were first described in 1936, and again in 1938.[1,2] More than 200 cases have now been reported and were reviewed recently.[3,4] The diagnostic criteria include: (1) normochromic, often macrocytic anaemia without reticulocytopenia, developing early in childhood; (2) bone marrow with normal cellularity and usually a deficiency of red cell precursors (although these are occasionally normal or even increased); (3) normal or slightly decreased leucocyte counts; (4) normal or often increased platelet counts. The original term, 'congenital hypoplastic anaemia' was used because it was thought that the marrow was hypoplastic. The eponym, 'Diamond-Blackfan anaemia' is useful, since it justifiably indicates no specific aetiology of the disorder.

The diagnosis is made most commonly in infancy. 25% of reported infants were anaemic at birth, 65% by 6 months, and 90% by one year. Rare cases were diagnosed between 2 and 6 years of age. The male:female ratio is one. Most reported cases are Caucasian, but Blacks, Orientals, and Indians have been reported.

The inheritance of Diamond-Blackfan anaemia is not clear. Three-quarters of the reported cases were sporadic. Two families had parental consanguinity, and 13 families had more than one affected child. Thus autosomal recessive inheritance was suggested. However, 6 families were reported in which there was anaemia in one parent. In 3 additional families, the fathers had more than one affected child by unrelated wives. In a few families, one child had Diamond-Blackfan anaemia, while a sibling or a parent had transient anaemia (see below).

Mothers of affected children have reported an increased incidence of miscarriages or stillbirths. 10% of such infants were born after problem pregnancies, such as toxaemia, haemorrhage, and a variety of illnesses. Low birthweight occurred in 10%, divided equally between preterm infants and those who were small for gestational age.

Physical anomalies were reported in approximately 30% of cases (Table 1). The most common finding is short stature. Other abnormalities are microcephaly, cleft palate, abnormal eyes, web neck, and deformed thumbs. The anomalies resemble those seen in patients with Fanconi's pancytopenia, but are usually not as prominent in the children with Diamond-Blackfan anaemia. Abnormal thumbs were reported in 20 cases.[5] 10 children had triphalangeal, and 7 had duplicated or bifid thumbs.

All patients are anaemic at the time of diagnosis. The anaemia is normochromic, but it is macrocytic in one-third. Reticulocyte counts are usually zero. White blood counts are normal or slightly decreased,

Table 1 *Physical findings in 229 patients with Diamond–Blackfan anaemia*

Abnormality	*No. of cases*
Height < 3rd centile	36
Microcephaly	9
Macrocephaly	2
Palate	
Cleft	12
High arched	3
Eyes	
Strabismus	6
Hypertelorism	8
Other (epicanthal folds, ptosis, blue sclerae, cataracts, microphthalmia)	14
Neck—short, and/or webbed	14
Thumbs	
Triphalangeal	10
Duplicated	7
Subluxed	2
Malformed	1
Mental retardation	9
Renal—caliectasis, partial horseshoe, double collecting system	7
Hypogonadism	5
Skeletal—scoliosis, Sprengel	3
Congenital heart disease	11
Ears—low set	7
Skin—café-au-lait spots	1
Toe syndactyly	2
At least one anomaly	60

Adapted from Alter[4].

while platelet counts are normal or increased. The patients' erythrocytes have several characteristics which define them as 'fetal': macrocytosis, increased fetal Hb and fetal membrane antigen i, as well as fetal patterns of red cell enzymes.[4,6] The bone marrow shows normal cellularity with erythroid hypoplasia in 90% of cases, while the rest have normal or hyperplastic erythroid development. Serum erythropoietin is increased, and most patients do not have serum inhibitors of erythropoiesis. Peripheral blood lymphocyte and bone marrow chromosomes are usually normal.

Cellular inhibition of erythropoiesis has been proposed but not confirmed as the pathophysiology of Diamond-Blackfan anaemia. Hoffman and co-workers found that the peripheral blood lymphocytes of 6 transfusion-dependent patients inhibited *in vitro* erythroid colony formation from normal bone marrow cells.[7] Steinberg and co-workers also observed suppressor lymphocytes in 2 patients.[8] However, Nathan and co-workers and Freedman and co-workers were unable to confirm this finding in a variety of patients.[9,10,11] Those patients who had inhibitory cells in the study of Hoffman had received multiple transfusions, and had presumably been sensitised to antigens which happened to be present in the normal bone marrows which were used in the experiments.[7] A similar problem has been reported in patients with acquired aplastic anaemia.[12]

The abnormality in Diamond-Blackfan anaemia appears to be in the erythroid stem cell. Null lymphocytes purified from peripheral blood contain erythroid progenitors, while T-lymphocytes produce soluble factors which stimulate *in vitro* colony formation from the null cell population.[13] Nathan and co-workers mixed null and T-cells from normal subjects with those from patients with Diamond-Blackfan anaemia.[14] T-cells from patients not only failed to inhibit, but actually stimulated erythroid colony formation from normal null cells. In contrast, null cells from patients failed to respond to normal T-cells. In other studies, *in vitro* erythroid colony formation from the bone marrow cells of patients with Diamond-Blackfan anaemia was decreased, and required unusually high levels of added erythropoietin. Thus the erythroid stem cell may have an abnormal response to the usual stimuli for erythropoiesis.

Patients with Diamond-Blackfan anaemia were initially treated by giving blood transfusions, and they died when these were stopped. Transfusions are still needed, at the time of diagnosis, and for about 20% of patients who do not respond to other forms of treatment. The current recommendation is that complete red cell typing be performed to reduce the possibility of sensitisation to red cell antigens. Frozen, washed, packed red cells should be used if possible. Hb should be kept above 6 g/dl, with transfusions every 4 or 6 weeks. The main complication from multiple transfusions is iron overload; this may be controlled with chelating agents.[15]

Administration of corticosteroids leads to a response in approximately three-quarters of the patients. Initial treatment is with prednisone, 2 mg/kg per day (given in three or four doses). Reticulocytes appear between one and 3 weeks later. Daily treatment is continued until Hb reaches 10 g/dl. The corticosteroid dose is then tapered, and treatment is given on alternate days. Most patients require from 1 to 40 mg prednisone on the treatment days, given as a single dose in the morning. A few puzzling patients respond to corticosteroids initially, but then fail to maintain erythropoiesis on doses that are less than toxic. Occasionally, a combination of low-dose corticosteroids plus androgens has been useful. One patient was engrafted successfully with a bone marrow transplant, but unfortunately died from pulmonary complications caused by haemosiderosis.[16] 20 to 30% of patients were reported to have spontaneous remissions from one to 16 years after the onset of their anaemia. The erythrocytes of most patients in 'remission', either corticosteroid-dependent or spontaneous, have fetal characteristics (see above), indicating that the patients are not cured of their underlying disease.

The reported mortality rate is approximately 15%, although it is undoubtedly higher. Most deaths were from complications of chronic transfusions and haemosiderosis—such as heart disease or pulmonary infections.

Recent reports have drawn attention to possible malignant complications. One patient developed hepatocellular carcinoma in a haemosiderotic liver.[17] Two patients died with acute myelogenous leukaemia as adults. One had been in a spontaneous remission from ages 16 to 32, after several hundreds of transfusions in childhood.[18] The other had received irradiation to long bones and thymus as a child, as well as many transfusions (L. K. Diamond, unpublished observations). One patient died with acute promyelocytic leukaemia; she had been transfusion-dependent, and had failed to respond to corticosteroids, cyclophosphamide, and androgens in the years before the leukaemia.[19] One child did respond to treatment for acute lymphocytic leukaemia.[20] The interrelations of an abnormal erythroid stem cell, haemosiderosis, and immunosuppressive drugs, form a currently unresolved matter of concern.

Acquired red cell aplasia: transient erythroblastopenia of childhood

Temporary anaemia, reticulocytopenia, and marrow erythroblastopenia have been reported in approximately 60 previously normal children (M. Link and B. P. Alter, unpublished observations). Transient reticulocytopenia is common in children with haemolytic disorders—such as hereditary spherocytosis or sickle cell disease—in whom anaemia is soon detected because of the short life span of the erythrocytes. The term 'transient erythroblastopenia of childhood' is restricted to those children who have no underlying haematological disease, and who recover. In Table 2 patients with this acquired and temporary anaemia are compared with those who have the constitutional permanent variety, Diamond-Blackfan anaemia. In the transient cases, a viral illness was usually noted 2 weeks to 2 months before diagnosis. All patients were between one month and 6 years of age, but 80% were between one and 4 years. The only unusual physical finding was pallor.

The blood shows anaemia, reticulocyte counts <1%, normal white blood counts, and normal or increased platelet counts (M. Link and B. P. Alter, unpublished observations). Red cell antibody tests are negative. Wang and Mentzer observed that patients with transient erythroblastopenia could be distinguished from those with Diamond-Blackfan anaemia because the erythrocytes of the former were adult in several features.[6] This distinction is useful at the time of diagnosis. However, patients with transient erythroblastopenia do produce erythrocytes with fetal characteristics during their recovery phase. This temporary fetal erythropoiesis resembles the chronic state of patients with Diamond-Blackfan anaemia (M. Link and B. P. Alter, unpublished observations). In transient erythroblastopenia, the bone marrow shows erythroid hypoplasia. Marrow culture *in vitro* did lead to normal erythroid colony formation in one study (B. J. Clarke *et al.*, unpublished observations); the erythroid cells which developed *in vitro* produced raised levels of fetal Hb. Recently, some patients with transient erythroblastopenia of childhood were found to have an IgG component in their sera which inhibits the growth of erythroid colonies in culture.[21]

Table 2 *Comparison of childhood red cell aplasias*

	Diamond–Blackfan anaemia	*Transient erythroblastopenia of childhood*
Number of reported cases	>200	60
Age at diagnosis	90%, <1 year	80%, 1 to 4 years
Aetiology	Constitutional	Acquired
Antecedent history	None	Viral illness
Physical examination	30%, abnormal (Table 1)	Normal
Laboratory		
Hb	2–4 g/dl	3–9 g/dl
White blood count	Normal	Normal
Platelet count $>400 \times 10^9$/l	80%	100%
MCV increased		
At diagnosis	30%	0%
After recovery	100%	90%
During remission	100%	0%
Hb F increased		
At diagnosis	100%	0%
After recovery	100%	100%
During remission	85%	0%
i antigen		
At diagnosis	100%	0%
After recovery	100%	60%
During remission	90%	0%

Adapted from Alter[4].

Recovery is usually apparent within one month of diagnosis. Many children require a single transfusion because of the anaemia. Corticosteroids have been used in cases in which the diagnosis was thought to be Diamond-Blackfan anaemia. However, permanence of recovery after corticosteroids were stopped led to the correct diagnosis. The transient fetal erythropoiesis noted above is independent of the mode of therapy.

Transient erythroblastopenia probably occurs frequently, as reticulocytopenia often accompanies viral illnesses. The disorder is only detected if Hb drops to symptomatic levels, or if blood counts are obtained before the onset of anaemia. Many children recover without any specific treatment, and anaemia does not usually recur with subsequent viral infections.

Acquired red cell aplasia: adult pure red cell aplasia

Many adults and a few adolescents have been reported to have developed pure red cell aplasia. The adult diseases have been reviewed extensively by Krantz and co-workers, and should be considered in paediatric cases.[22,23,24,25] Half the adults had an associated thymoma; the male:female ratio is 1:2 in those with, and 2:1 in those without this association. A few patients had malignancies. Children have been reported who developed red cell aplasia during treatment for leukaemia.[26] Many of the adults have had laboratory evidence of autoimmune disorders.

The anaemia is normochromic and normocytic, with reticulocytopenia. White blood counts and platelet counts are normal or decreased. Bone marrows show normal cellularity and erythroid hypoplasia. Autoimmune manifestations have included antibodies to red cells, smooth muscle, and intrinsic factor, as well as antinuclear antibody and paraproteins. Soluble inhibitors of erythropoiesis have been demonstrated in the IgG fraction from several patients. These antibodies have inhibited *in vitro* heme synthesis, and *in vitro* erythroid colony formation from normal marrow precursors. In some cases, the inhibitors were cytolytic to erythroblasts. A few patients had antibodies to erythropoietin.

The main treatment is transfusion. Thymectomy may be helpful in those with a thymoma. Splenectomy has had limited success. Chemotherapy has included corticosteroids, cyclophosphamide, azathioprine, and 6-mercaptopurine, and one, or a combination of these, has occasionally led to a remission. However, a guarded prognosis must be given to patients with the adult form of acquired red cell aplasia.

Conclusions

The form of red cell aplasia with the best prognosis is transient erythroblastopenia of childhood. Children acquire this anaemia rapidly, due to transient cessation of erythropoiesis. They also recover rapidly and apparently permanently. They exhibit temporary fetal erythropoiesis, similar to that seen in any type of stress erythropoiesis, but this disappears. Specific studies of erythropoiesis are incomplete because of the rapid course and rarity of patients. Although soluble or cellular inhibitors of erythropoiesis may be involved in some cases, the most likely aetiology is a failure of development of erythroid progenitors.

In adult pure red cell aplasia the disorder is long-lasting although there have been recoveries. Soluble inhibitors of various levels of erythropoiesis have been detected routinely. The erythroid progenitor cells themselves are apparently normal.

Constitutional red cell aplasia is apparently due to an abnormality in the erythroid stem cell itself. Most studies have failed to demonstrate soluble or cellular inhibitors of erythropiesis. Treatment with corticosteroids leads to a partial correction of the erythropoietic defect, perhaps by improving the interaction of erythropoietin with erythropoietin-responsive stem cells. Further studies are required to define the abnormality more specifically. Meanwhile, patients with red cell aplasia of any except the most transient variety must be followed up because of the possibility of belated haematopoietic developments.

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A better deal for newborns with congenital heart disease

Despite the great strides made in management of heart diseases in children during the last 25 years, these still account for more deaths in infancy than all other congenital anomalies put together.[1,2] Furthermore in population studies on necropsy, it has repeatedly been shown that of deaths certified as due to congenital heart disease, about two-thirds were within the first year of life and about half of these were during the first month.[3] Population necropsy studies tend to present a gloomier prognosis than those based on diagnosis in life as well death. Nevertheless, in a study of the latter type carried out as recently as 1968–72, it was shown that, even when patients with severe associated congenital lesions were excluded, only 61% of infants with congenital heart disease survived the first year.[4] Effective prevention of congenital heart disease seems unlikely to emerge within the next decade, so that any policy designed to reduce death and disability from congenital heart disease must at present be focused on management during the early months of life. The paper by Izukawa *et al.*[5] (page 281) documents in a heartening manner the improvement in life expectancy that has occurred in newborns with structural heart disease in the last decade treated at their hospital, which acts as a referral centre for a large part of Canada.

In a number of committee reports on resources for management of heart disease in children, the principle has been accepted that in order to provide optimal standards of care, a limited number of specialist centres are required.[6,7,8,9] A revised report of the Joint Cardiology Committee is about to be published, taking the same view. This annotation will summarise the evidence supporting this view, and argue that in order to provide the best service for newborn babies with congenital heart disease, it is necessary to think in terms of creation of supraregional centres specialising in the care not just of newborns, but also of infants.

The reasons for the improvement in survival of newborns from Toronto[5] are, in brief, experience and expertise. While these do not always go together, they usually do. Particularly strong evidence for this assertion comes from a study carried out in London during the period 1969–71 of centres treating infants with congenital heart disease.[10] 13 such centres were identified as being involved in infant cardiac catheterisation and surgery; 2 of these performed 69% of all cardiac catheterisations and 76% of all operations. The combined operative survival for infants from the 2 centres was 72%, whereas the corresponding figure for the remaining 11 was 54% ($P<0 \cdot 001$). Furthermore, patients in the 2 centres were less likely to die at cardiac catheterisation, and more likely to have a corrective than a palliative operation. And this was despite the fact that both centres were seeing a population of infants with more serious congenital heart disease than were the others. So expertise is fundamental, but experience and therefore size cannot be ignored in planning cardiological services.

The incidence and severity of congenital heart defects is similar in America and England.[11,12] Therefore the size of the British problem can be defined very precisely from the New England Regional Infant Cardiac Program.[13] Case finding in that study[14] is almost certainly higher than that from any comparable British study. In New England there is a mixture of units, some aggressive and some more conservative in their management, much as there is in this country, so that projections of work load from their experience are probably quite reasonable for the UK.

The number of live births in England and Wales in 1974 was 603 140. A survey of 16 centres in England and Wales carrying out infant cardiac catheterisations showed that 47% of these were in neonates.[15] To these facts are added the following from the New England study:[4,13,14]

(1) The incidence of heart disease presenting in infancy and requiring cardiac catheterisation (2·7 per 1000) (D. C. Fyler, 1978, personal communication).

(2) The proportion of infants catheterised requiring operation in infancy (58%).

(3) The proportion of infants with severe associated anomalies precluding cardiac surgical intervention (10%).

From these figures it appears that each year 1470 (29·4 per million population) infant cardiac catheterisations and 850 infant operations can be expected from England and Wales. About 425 (8·5 per million) of these operations would be open heart ones.

The number of neonatal catheterisations is a very reliable indicator of patients referred, since essentially all catheterisations in this age range are emergencies, carried out in seriously ill babies. This number, predicted from the above figures, is 690 (13·8 per million) per annum for England and Wales. In the British survey,[15] 16 major centres reported an average of 365 neonatal catheterisations per year (1971–75). One large centre reported a further 54, too late for inclusion, but it is difficult to believe that the overall total from every centre in England and Wales could exceed 500 per annum. This leaves the total figure still 190 short of the prediction. This large shortfall can hardly be accounted for by the fall in birth rate, particularly as the total number of catheterisations performed did not change during the survey period. Nor does it seem likely that the problem lies in applying American figures to British patients. The possibility must be faced that about 25% of neonates with congenital heart disease in this country are still being neither adequately investigated nor treated. Why should this be? The most likely answer is that there is insufficient awareness of the possibilities of effective, curative treatment in specialist centres.

Let us leave aside the question of shortfall, and assume that there is none for the purpose of determining how many specialist centres are required. Successful management of infants with serious congenital heart disease is a matter of highly coordinated team work involving technical staff, specially trained children's nurses, experts in anaesthetics, ventilation, radiology, and nephrology, as well as paediatric cardiologists and cardiac surgeons. At any level, lack of sufficient experience prejudices the outcome. It may well be that no centre in the UK has yet reached an optimal level of activity. However, a minimum is probably one infant open heart operation per week on average. Open heart surgery is chosen as the paradigm because it is the most demanding on personnel. To achieve the predicted requirements, only 8 centres in England and Wales would be necessary. However, two surgeons per centre are required to maintain 24-hour cover. Sharing the work load, each would only do one infant open heart operation a fortnight. Most surgeons would not regard this as adequate to maintain standards, so the optimal number of centres required in England and Wales is probably less than 8, particularly as these figures have been calculated for predicted rather than actual work load.

Supraregional centres along the lines proposed would not, of course, limit their activities to infants. If they were to do so, there would be an insufficient total volume of work, and what work there was would be of such complexity that it would make impossible demands on the personnel of such a unit. A much wider age range of patients would be treated.

This figure for the number of supraregional centres required is uncomfortably low, and specialisation of this order would undoubtedly introduce new problems. What are they, and would they outweigh the benefits?

The first disadvantage is of course that there would be a lot of travelling for the baby and relatives. This will never be a pleasant experience, but then neither is the unnecessary death of the baby. We (and doubtless others) have found that it is possible for a young infant to suffer several cardiac arrests outside the UK, and yet to survive a long air flight and corrective surgery in this country. This illustrates graphically that transport need not be hazardous provided that the means to maintain thermal, fluid, and acid-base balance, together with ventilation (if necessary), are initiated before the journey.

At the moment, such care is undertaken by the referring nonspecialist hospital. In the future, the responsibility for this kind of action may come to rest with the specialist centres, along the lines developed by general neonatal intensive care units.[16,17] But because of the far greater distances, this would place demands upon the medical and nursing personnel in the specialist centres that would be extremely heavy, and certainly beyond the present capabilities of any unit of this type in the country.

Of particular concern, as so many of these emergencies occur in the first few days of life, is that the baby may be transported, but the mother is not. This inevitably impairs primary bonding and establishment of breast feeding. This is perhaps particularly unfortunate if the physical condition of the baby turns out not to be serious. These problems would, in my view, be greatly alleviated by a 2-pronged strategy. Firstly, paediatric cardiologists would have to take more seriously their educational role with regard to budding (or even not so budding) paediatricians and neonatologists, as these play such a vital role in screening for serious structural heart disease. This would not only reduce unnecessary referrals (which are in any case rare), but, more importantly, help to ensure earlier referral of serious heart disease before the baby's condition becomes critical. Secondly, mothers could be encouraged more often to accompany their babies (particularly if they have no other children) and would be actively helped to do so, even if it meant extra medical care for the mother.

Cardiac catheterisation and surgery are not cheap when viewed in isolation, but there can hardly be another specialty where such sick individuals are so completely restored to normality for such a long time. So the cost-benefit ratio, insofar as this can be quantified, is probably low compared with many other widely performed procedures. All in all, the benefits of supraregionalisation of infant cardiac care far outweigh the disadvantages, provided that the latter are minimised along the lines suggested.

It is true that in 1979, now that some lesions can be repaired in infancy with an immediate survival of better than 95% in a few centres, that the residual problems are becoming more and more concentrated in the first month of life.[18] But for three reasons, my view is that it would be a mistake at this stage to create neonatal rather than infant supraregional centres. Firstly, the number would be too small. Secondly, open heart surgery in later infancy is still far from routine even in specialist centres. Thirdly, some of the numerically most important conditions causing serious cardiac disability and death in infancy do not normally present until the 2nd and 3rd month of life, notably ventricular septal defect. Since it has been clearly shown that in certain centres, primary closure of the defect in infants with intractable cardiac failure carries a lower early and late mortality than banding of the pulmonary artery,[19,20] there seems to be a good argument for the creation of centres where such open heart approaches to treatment may become routine. At this time, only a few such hospitals in this country have established reputations in the field, so that recognising these as supraregional centres would not be difficult. The longer action along these lines is delayed, the more centres will become involved. Rationalisation could then become painful to the point at which it would never happen. The arguments put forward will perhaps have convinced even the sceptical that this would be a pity.

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Diagnosis and management of folate deficiency in low birthweight infants

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SUMMARY Significant folate deficiency in 14 out of 37 preterm infants of birthweights 2·0 kg or less was found to be reliably and most conveniently diagnosed by abnormal morphological changes in peripheral blood and confirmed by the response to folic acid. Deficiency appeared to be more common in light-for-dates infants including the smaller of twins. Neither the clinical status nor the levels of haemoglobin or erythrocyte folate was a reliable guide to the presence of megaloblastic erythropoiesis in the very young preterm infant. 100–200 μg folic acid a day, orally or IM, may be required to ensure an optimal haematological response, and this would be appropriate for therapeutic trial if the diagnosis is in doubt. This amount would also replenish tissue folate stores; larger doses are likely to exceed the requirements of small infants.

In an earlier paper (Strelling *et al.*, 1966) we drew attention to the vulnerability of premature infants to folate-responsive megaloblastic anaemia. The most appropriate dose of folic acid for the treatment of affected infants is however unknown. The effect of varying amounts of folic acid on 19 infants is reported, in whom the morphology of the peripheral blood was either frankly megaloblastic or highly suggestive of such change. The diagnosis of folate deficiency in the very young low birthweight infant and the value of a therapeutic trial with small 'physiological' amounts of folic acid are also considered.

Materials and methods

The infants with observed or suspected megaloblastosis were discovered during the course of an investigation into the folate status of approximately 100 infants between birth and 12 months. 37 of these fulfilled the following criteria: (a) gestation <37 completed weeks*, (b) birthweight 2·0 kg or less*, (c) unaffected by a major congenital abnormality or haemolytic disease. They were as far as possible consecutive admissions to a special care baby unit.

24 were term (38–42 completed weeks), normal, singleton infants from uncomplicated 1st or 2nd pregnancies weighing at least 3·0 kg at birth selected as controls with informed parental co-operation. All these infants thrived.

None of the mothers in either group of infants had been folate-deficient or had received folic acid supplements during pregnancy.

Feeding. The preterm infants were fed evaporated milk (Carnation) changing to full-cream dried milks when their weights had reached 2·5 kg. From the 3rd week they were given 22 mg elemental iron in 4 ml sodium iron edetate (Sytron, Parke-Davis) and 7 drops of a multivitamin preparation not containing folic acid (Protovite, Roche) each day. All except 2 control infants who were breast fed received dried milk feeds. The milks were sterilised by autoclaving after reconstitution.

Investigations. Blood was taken by heel prick just after birth, repeated at 2 to 4 weeks, and at least twice during weeks 5 to 10. Further samples were

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*One infant of 37 weeks and one of birthweight 2·06 kg with suspected megaloblastosis were included.

taken during weeks 11 to 20 and between months 6 and 12. The following examinations were made: Hb, MCHC, reticulocytes, PCV, and films. Buffy coat smears were taken from microhaematocrit preparations spun relatively slowly (750 rev/min) for 5 minutes.

Assays of whole-blood folate (*L. casei*) were made on duplicate samples of 50 µl blood using the method described previously (Strelling *et al.*, 1966), red-cell folate being calculated from the haematocrit.

Abnormal haemopoiesis was assessed on blood and buffy coat smears as: (1) *megaloblastic*; the presence of megaloblasts or transitional megaloblasts with eosinophilic or polychromatophilic cytoplasm, or (2) *suspected megaloblastic*; orthochromatic oval macrocytes, macronormoblasts, and hypersegmented neutrophils. Marrow biopsies were not taken.

Folic acid treatment. Folic acid was given daily as follows: (1) 5 mg IM (6 infants) and orally (1 infant), (2) 1–2 mg orally (4 infants), (3) 60 µg IM (2 infants) or 50 µg orally (2 infants), and (4) 15–120 µg IM initially, the amount being increased every few days depending on the haematological response (4 infants).

As only 5 mg tablets of folic acid were available both 1 mg and 50 µg tablets of folic acid were prepared commercially. A parenteral folic acid solution containing 15 mg/ml (Folvite, Lederle) was appropriately diluted immediately before each IM injection.

The haemopoietic response was assessed on the reticulocyte count, blood films, and buffy coat smears.

Birthweight/gestation centiles. These are from the data of (1) Thomson *et al.* (1968) for infants born after 31 completed weeks, allowing for sex and parity, (2) Babson *et al.* (1970) for infants born between 28 and 31 completed weeks.

Results

Findings in low birthweight infants. Megaloblastosis was observed in 19 of the preterm infants with birthweights of 2 kg or less. Data on these infants are shown in Table 1. In 14 the diagnosis was confirmed by the haematological response to treatment with folic acid, but this was suboptimal in 4 (Cases 15–18) and was not assessed in one (Case 19). The remaining 18 low birthweight infants showed no morphological evidence of folate deficiency, and none of the 6 who received a trial of folic acid showed any haematological effect. Data on these infants and the controls are shown in Table 2.

Nine (64%) of the confirmed megaloblastic group had birthweights below the 10th centile compared with 5 (28%) of the normoblastic group. In all the 45 infants who were below 37 weeks' gestation irrespective of birthweight, there were significantly more who were light-for-dates in the megaloblastic group ($P<0\cdot05$).

Hb was invariably below 10 g/dl in the megaloblastic infants at diagnosis but it was also at this level in 13 of the 18 normoblastic infants. The mean difference in Hb at average age 7 weeks was 1·1 g/dl, values in the megaloblastic group being significantly lower ($P<0\cdot05$, Table 2).

Erythrocyte folate levels in 22 of the 37 low birthweight infants at average age 7 weeks were below those in controls of comparable postnatal age ($P<0\cdot05$, Table 2). Values in 3 infants with confirmed or suspected megaloblastosis and in 5 of the normoblastic low birthweight group were nevertheless within the control range.

None of the control infants at any time and no low birthweight infant over 12 weeks showed any cytological evidence of folate deficiency on peripheral blood examination. Three of the normoblastic low birthweight infants who did not receive folic acid had erythrocyte folate levels <100 µg/l at 6 months.

The condition of no infant caused undue concern when morphological evidence of folate deficiency was found, although in 4 there had been previous clinically mild infections of the urinary or respiratory tracts.

Serum vitamin B12 values (*Lactobacillus leichmanni*) in 5 low birthweight infants were 150–335 ng/l (normal 160–950 ng/l).

Treatment with folic acid.

Standard doses (1–5 mg daily)

An unequivocal response occurred in all 6 infants given 5 mg folic acid daily IM (Cases 1–6) and in 3 of the 4 given 1 or 2 mg orally (Cases 7–9). Blood films and buffy coat smears examined between days 3 and 7 showed normoblastic transformation and a pronounced increase in polychromatophilic erythrocytes. Reticulocytes were often slightly increased before treatment but a definite subsequent rise was nevertheless demonstrable. Enlargement of spleen and/or liver was noted in several infants after treatment with folic acid; the reason for this was not clear.

The haematological response was suboptimal in Case 15 (5 mg/day orally) and was not assessed in Case 19 (2 mg/day orally).

Whole-blood folate was estimated in 4 megaloblastic infants receiving 5 mg/day folic acid IM and

Table 1 *Findings in 19 infants with observed or suspected megaloblastosis and the results of treatment with folic acid*

	Birth data				*Findings at diagnosis*					*Results of folic acid treatment*					
Case	*Sex*	*Gestation (weeks)*	*Birthweight (kg)*	*Twin or triplet*	*Age (weeks)*	*Hb (g/dl)*	*PCV*	*Morphology*	*Erythrocyte folate (µg/l)*	*Reticulocytes (%)*		*Rise over 2–4 weeks*		*Effective dose*	
										Before	*After*	*Hb*	*PCV*	*Mg/day or µg/day*	*Route*
1	F	30	1·42		10	6·2	—	M		1	15	4·9	–	5 mg	IM
2	F	33	1·30*	Twin 1	7	5·4	20	M	90	1	7	3·3	9	5 mg	IM
3	F	35	1·40*	Twin 1	7	7·7	24	M	37	2	18	2·6	8	5 mg	IM
4	F	35	1·38*	Twin 2	7	8·4	25	M	37	1	5	0·9	3	5 mg	IM
5	M	33	1·86	Twin 1	5	8·0	22	M	42	2	4	0·6	2	5 mg	IM
6	F	33	1·34*		8	8·0	22	SM	68	0	7	1·3	5	5 mg	IM
7	M	35	1·24*	Twin 1	7	9·5	28	M		3	14	1·8	–	2 mg	Oral
8	F	36	1·58*	Triplet 1	6	9·2	25	M		6	12	0·6	4	1 mg	Oral
9	F	36	1·60*	Triplet 2	6	8·5	23	M		4	14	1·1	6	1 mg	Oral
10	M	32	1·56		7	8·1	21	M	150	7	14	1·5	6	120 µg	IM
11	M	35	1·78*		6	9·1	28	M	168	3	14	0·9	0	120 µg	IM
12	F	28	0·98		12	8·6	26	SM		1	12	1·2	1	60 µg	IM
13	M	29	1·14		6	8·5	26	SM		2	16	0·3	–	60 µg	IM
14	F	35	1·56*		7	7·8	21	SM		4	13	1·3	8	50 µg	Oral
Not confirmed															
15	M	30	1·57	Twin 1	7	8·3	—	SM		–	7	1·6	–	5 mg	Oral
16	F	33	2·06		7	9·1	25	SM	64	3	7	0·8	4	120 µg	IM
17	F	31	1·35		11	10·0	30	SM	67	2	3	1·3	3	240 µg	IM
18	F	37	1·22*	Twin 2	9	9·4	30	SM		6	6	0·8	2	50 µg	Oral
19	F	32	1·50		7	9·1	25	SM	120	2	—	—	–	2 mg†	Oral

*Birthweight < 10th centile. †Response not assessed. M = Megaloblastic; SM = suspected megaloblastic.

Table 2 *Birth data and findings between 5 and 12 weeks in megaloblastic and nonmegaloblastic infants <2 kg birthweight and in controls*

Infants	*Gestation (weeks)*	*Birthweight (kg)*	*<10th centile*	*Twins or triplets*	*Age (weeks)*	*Hb (g/dl)*	*PCV**	*MCHC* %*	*Reticulocytes* %*	*Erythrocyte* folate (µg/l)*
Megaloblastic (n = 14 confirmed)										
Mean	33·2	1·43	9	7	7·2	8·1	23·9	34·4	2·6	87†
Range	29–36	0·98–1·86			5–12	5·4–9·1	20–28	31–37·1	<1–7	37–168
Normoblastic (n = 18)										
Mean	33·2	1·78	5	9	7·6	9·2	26·3	34	2·6	101‡
Range	30–36	1·51–2·0			5–10	6·7–11·1	20–31	31·1–35·2	<1–4	50–214
Controls (n = 24)										
Mean	40	3·49	—	—	7·9	11·8	33·4	35·4	<1	237
Range	38–42	3·05–4·5			5–10	10·6–12·8	29–37	32·7–37·3	1–3	110–655

*Haematological values and erythrocyte folate taken when Hb at lowest point. †7 values, ‡ 15 values.

in 12 further infants of birthweights 2·0–3·0 kg receiving 5 or 10 mg/day orally. Values >1000 µg/l were invariably found. These were not assayed precisely in this high range but would almost certainly have produced red-cell folate values well above normal. Erythrocyte folate assayed after stopping treatment declined slowly; at an average age of 7 weeks later the mean value in 11 infants was 828 µg/l (405–1406 µg/l).

Unchanging small doses

Both infants given 60 µg/day of folic acid IM (Cases 12 and 13) and one of the 2 given 50 µg/day orally (Case 14) showed a brisk normoblastic and reticulocyte response; erythrocyte folate was not measured. The response to 50 µg/day of folic acid orally in the 4th infant (Case 18) was difficult to assess as the abnormal morphology had improved spontaneously in the week before treatment when the reticulocytes were 6%.

Increasing small doses

In an attempt to find a minimum effective therapeutic dose, 4 infants were given progressive increments of folic acid while the morphology and red-cell folate were monitored. Details are given below.

Case reports

Case 10 (Figure). A baby boy, birthweight 1·56 kg, 32 weeks' gestation. At 7 weeks Hb 8·1 g/dl, PCV 22, and erythrocyte folate 150 µg/l. Transitional megaloblasts were noted in buffy coat smears and, 2 days later, true megaloblasts. The reticulocytes had begun to rise (7%) before folic acid was started.

15 µg folic acid IM for 3 days and 60 µg IM for 2 days produced no haematological response and megaloblasts persisted. Two doses of 120 µg/day IM were followed by an increase in polychromatic erythrocytes, and these and normoblasts were smaller. Megaloblasts disappeared and reticulocytes rose to 10% although the erythrocyte folate fell slightly to 122 µg/l. This response continued for a further 7 days with a peak reticulocytosis of 14% after 10 × 120 µg folic acid IM when the erythrocyte folate was 530 µg/l. The intensity of response then diminished gradually despite increased dosage.

Comment

A haematological response and a rise in erythrocyte folate was obtained with 120 µg/day folic acid IM.

Case 11. A baby boy, birthweight 1·78 kg (<10th centile), gestation 35 weeks. At 6 weeks Hb 9·1 g/dl, PCV 28, reticulocytes 3%. Transitional megaloblasts and slightly increased polychromasia on blood films.

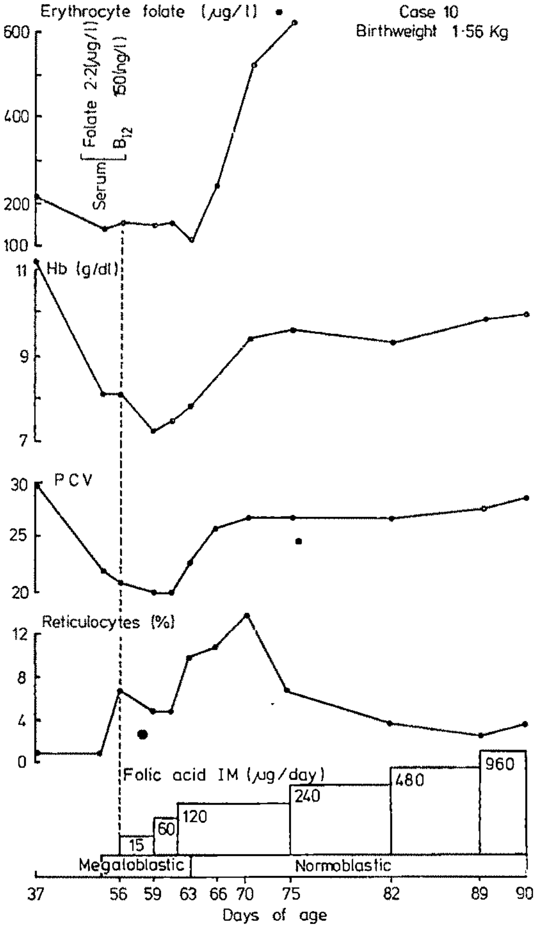

Figure *Treatment of megaloblastic anaemia in a preterm infant with increasing small doses of folic acid.*

Erythrocyte folate 168 µg/l. Folic acid 60 µg/day IM produced a moderate normoblastic response with reticulocytes of 5% on day 2 rising to 14% on day 7.

Erythrocyte folate was 167 µg/l on day 6 but fell to 108 µg/l on day 15 so the folic acid was increased to 120 µg/day IM. The reticulocytes remained raised until 6 weeks after beginning treatment.

Comment

Although a good haematological response occurred on 60 µg/day folic acid IM the erythrocyte folate declined; 120 µg/day might have been the appropriate dose.

Case 16. A baby girl, birthweight 2·06 kg, gestation 33 weeks. At 7 weeks folate deficiency was suspected, Hb 9·1 g/dl, PCV 25, reticulocytes 3%. Erythrocyte folate was low at 64 μg/l. A week later the morphology was less abnormal, Hb 9·9 g/dl, reticulocytes 5%, and erythrocyte folate 88 μg/l. Folic acid 60 μg/day was given IM and although polychromatic cells and reticulocytes increased slightly (7%), the response was not definite. As the erythrocyte folate had fallen to 40 μg/l on day 7, folic acid was increased to 120 μg/day IM.

Case 17. A baby girl, birthweight 1·35 kg, gestation 31 weeks. At 11 weeks folate deficiency was suspected on blood films which showed pronounced neutrophil hypersegmentation. Hb 10 g/dl, PCV 30, reticulocytes 2%. Erythrocyte folate was low at 67 μg/l. A week later without treatment the morphology was less abnormal, Hb 9·6 g/dl, PCV 27, reticulocytes 4%. Erythrocyte folate had risen to 140 μg/l. There was a slight haematological response after 3 days of treatment with folic acid 120 μg/day IM. As the erythrocyte folate had fallen to 86 μg/l the dose was increased to 240 μg/day IM for a further 3 days.

Comment

Morphological abnormalities improved in Cases 16 and 17 before treatment. The haematological response to 60 μg/day IM (Case 16) or to 120 μg/day IM (Case 17) was suboptimal. Erythrocyte folate fell in both infants, suggesting these amounts fell short of requirements.

Discussion

Diagnosis. Megaloblastic haemopoiesis may be overlooked in small infants. Clinical pointers to severe folate insufficiency which might have been expected—such as pallor, poor feeding, slow weight gain (Gandy and Jacobson, 1977), or severe infections (Gray and Butler, 1965)—were generally absent when the diagnosis was made and earlier infections in a minority of infants had been clinically mild. Neither Hb nor erythrocyte folate level was found to be a reliable guide to megaloblastic haemopoiesis. No affected infant had Hb >10 g/dl but only a few were significantly anaemic for infants of comparable birthweights and ages (Lundstrom *et al.*, 1977). Megaloblastosis however developed at an average age of 7 weeks when the effect of folate deficiency on Hb level is likely to be masked by such major physiological variables as red-cell mass at birth, postnatal depression of erythropoiesis, and rate of growth. The erythrocyte folate often fell during the 2nd and 3rd months to subnormal levels in both normoblastic and megaloblastic infants <2 kg birthweight, but values did not necessarily reflect the true severity of folate depletion. These were within the range found in term healthy controls (110–655 μg/l) in 2 infants with confirmed and one with suspected megaloblastosis, presumably due to the survival of erythrocytes formed during the perinatal period of relative folate affluence.

On the other hand, a clinical feature not previously described is a possible relationship between low birthweight for gestational age and the subsequent development of megaloblastic anaemia, for there was an undue proportion of preterm infants who were light-for-dates (<10th centile) among the megaloblastic group. Moreover, in 2 twin pregnancies only the smaller of each pair was affected. The reason for this is uncertain: limited fetal acquisition of folate or relatively rapid postnatal growth (Gairdner and Pearson, 1971) may well be contributory factors. An association between erythroblastosis, rate of weight gain, and folate insufficiency in infants up to one year has been reported (Gandy and Jacobson, 1977). While we were unable to find megaloblastic haemopoiesis in a group of erythroblastotic infants studied from birth, there was a haematological response after folic acid treatment in 2 affected preterm infants who had become severely anaemic at 3 and 5 weeks (Strelling, 1977).

The mainstay of diagnosis of folate deficiency was abnormal morphology using the buffy layer of capillary blood centrifuged slowly to concentrate abnormal cells, particularly the megaloblasts. While morphological abnormalities were sometimes shortlived and were not found in any case beyond 12 weeks, a search for them appears essential to the evaluation of the folate status of very young preterm infants.

Prevention. Whether folate insufficiency affects the somatic growth or neurological development of preterm infants is unknown. Lack of the vitamin limits the synthesis of thymidylate, a necessary precursor of DNA, megaloblastosis representing a stage at which DNA replication has become deranged (Hoffbrand *et al.*, 1976). Deficiency not severe enough to produce megaloblastosis may nevertheless impair growth, as shown in erythroblastotic infants by Gandy and Jacobson (1977). Dallman (1974a) estimated that preterm infants need 50–70 μg (25–35 μg/100 kcal) of folate a day. Neither the newer ready-to-feed proprietary milks (3·2–3·5 μg/100 ml*) nor fresh human milk (average 5·4 μg/100 ml, Ford and Scott, 1968) is likely to supply more than 10–20 μg/day of folate to very low weight infants over the first 8 weeks. Evaporated milk given to the infants in this study may have provided even less, for such milk with a relatively small ascorbic acid content tends to lose heat-labile folate through sterilisation (Ford and Scott, 1968). As preterm infants are vulnerable to deficiency during a period of rapid growth and cell replication, we would continue to advocate that folic acid supplements of about 50 µg/day be given to those under 2 kg for the first 3 months to ensure an ample supply for growth and development.

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*Manufacturers' reports.

Treatment. There is little information on the optimal amount of folic acid required for the treatment of preterm infants with megaloblastic anaemia. Recommended doses generally vary between 500 µg (Dallman, 1974b) and 2–5 mg (Smith, 1972; Pearson, 1975) a day, although Willoughby (1977) suggests that 200 µg may be enough in uncomplicated cases.

We found that 5 or 10 mg/day folic acid either orally or IM produced high blood folate levels and was clearly in excess of the requirements of small infants; an oral dose of 1 or 2 mg gave an equally good haematological response.

Daily doses of between 50 µg orally and 120 µg IM also produced an optimal haematological response in 5 out of 8 infants tested. The response to the same dose in the other 3 was suboptimal, possibly because morphological abnormalities had improved and reticulocytes begun to rise before treatment was started.

Erythrocyte folate was monitored in 4 of the 8 infants given small doses of folic acid. 60 µg/day IM was accompanied by falling levels in 3 infants, in one of whom increasing the amount to 120 µg produced a satisfactory rise. The same dose was associated with a drop in folate in the 4th infant.

Hence, although an excellent haematological response may follow as little as 50 µg/day folic acid, this amount is unlikely to meet the demands of increased haemopoiesis and, at the same time, replenish the infant's stores of folate. Needs may also vary and a full haemopoietic response may not always occur on this amount. Therefore the optimal therapeutic dose of folic acid is probably in the region of 100–200 µg/day orally or IM. Crystalline folic acid (pteroylmonoglutamic acid) was well absorbed orally in the small infants but suitable small dose oral or parenteral preparations are not readily available in the UK.

It may be considered whether treatment with excess folic acid could be potentially harmful, especially to the immature brain. Although folic acid has potent convulsive effects in experimental animals when injected directly into CSF or the brain (Hommes and Obbens, 1972) there appears to be an efficient homeostatic mechanism in the blood–brain barrier which helps maintain CSF and probably brain levels of folate within relatively narrow limits (Spector and Lorenzo, 1975). The main objection to the use of excess folic acid appears to be if vitamin B12 deficiency were present. A suboptimal haematological response may then follow treatment with large doses of folic acid and there is at least a theoretical risk that such treatment may precipitate central nervous system damage. Thus brain damage associated with congenital vitamin B12 deficiency has been reported (Pearson *et al.*, 1964; McNicholl and Egan, 1968); 4 of these infants with congenital deficiency of intrinsic factor had been treated with large amounts of folic acid (Strelling, 1969). There is insufficient information concerning the vitamin B12 status of preterm infants. 14 out of 24 such infants in one report (Pathak and Godwin, 1972) had subnormal serum levels although values in 5 low weight infants in this study were in the low normal range.

It may be concluded that significant folate deficiency in infants <2 kg birthweight may be reliably and most conveniently diagnosed on abnormal morphological changes in peripheral blood and adequately treated with 100–200 µg/day folic acid, orally or IM. The haematological response to this amount would also serve as a therapeutic trial when the diagnosis is in doubt.

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New technique for servo-control of arterial oxygen tension in preterm infants

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SUMMARY Equipment has been developed for the servo-control of arterial oxygen tension in sick, newborn babies. Using an indwelling umbilical arterial oxygen electrode as sensor, the equipment successfully regulated the administration of oxygen to 12 newborn babies with respiratory distress syndrome, significantly improving the stability of arterial oxygen tension and lessening the duration of episodes of hypoxia and hyperoxia.

In recent years, the continuous monitoring of oxygen tension in sick, preterm babies has been made possible by the development of miniature polarographic electrodes. Arterial oxygen tension (Pa_{O_2}) can be measured using an umbilical catheter-tip electrode, or transcutaneously using a heated skin-surface electrode. Thus, the twin hazards of prolonged hypoxia (Stewart and Reynolds, 1974), and hyperoxia (Ashton *et al.*, 1953), can be avoided by manual adjustments to the fractional inspired oxygen concentration ($F_{I}O_2$) when Pa_{O_2} deviates from within safe limits.

When Pa_{O_2} is continuously monitored in sick, preterm babies, pronounced fluctuations can be seen to occur within short periods of time, although intermittent blood–gas analysis may indicate a steady state. Fluctuations may occur spontaneously, or result from routine nursing or other procedures (Speidel, 1978), and such changes in Pa_{O_2} together with alterations in heart rate and blood pressure may be responsible for intracranial haemorrhage in some cases (Wigglesworth and Pape, 1978). Correction of these fluctuations by the manual adjustment of $F_{I}O_2$ requires constant, time-consuming observation. It seemed obvious to try to automate this procedure and we describe the application of a prototype machine for the automatic control of Pa_{O_2} in sick, preterm babies.

Patients and methods

12 preterm babies with respiratory distress syndrome were studied in the first week of life. Their birthweights ranged between 760 and 2260 g (mean 1640) with gestational ages between 26 and 34 weeks (mean 31·3). The main items of equipment and their arrangement are shown in the Figure.

In each case, Pa_{O_2} and $F_{I}O_2$ were continuously monitored using an indwelling umbilical artery catheter-tip electrode (Searle) and an oxygen analyser (Hudson). The umbilical catheter was continuously flushed with dextrose/saline at a rate of 0·5 ml/hour. Its reading was checked at least 4-hourly by formal blood–gas analysis (I.L. 213 blood–gas analyser), and adjustments were made as necessary. The largest adjustment required during the study period was 1·6 kPa (12 mmHg).

The output of the Pa_{O_2} electrode was fed into the servo-control unit, the technical details of which are

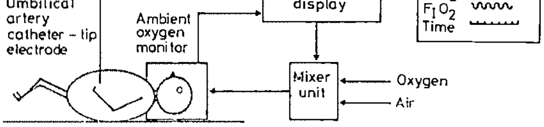

Figure *Arrangement of apparatus and equipment*

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presented in a separate paper (Collins *et al.*, 1979). At 1-min intervals, the reading was compared with the preset limits for Pao$_2$: lower limit 7·3 kPa (55 mmHg), upper limit 10·7 kPa (80 mmHg). If the Pao$_2$ was outside these limits, the servo-control unit adjusted the F_IO_2 (by means of a BOC air/oxygen mixer tap) by a single step of 5%. Thus, automatic adjustments of F_IO_2 were made at 1-min intervals if necessary. If 3 successive steps (i.e. 15% change in oxygen requirements) in either direction occurred, alarms were activated. Any defect developing in the function of the catheter-tip electrode would cause such successive steps in F_IO_2 to be made, and would therefore lead to activation of the alarms. Thus, the alarm would indicate failure of the equipment, disconnection of tubing supplying oxygen to the infant, or a change in the clinical state of the baby—such as a pneumothorax. In the event of mains failure, a preset F_IO_2 would continue to be provided and in an emergency any desired F_IO_2 could be obtained by pressing a button.

Using a multichannel chart recorder (Devices), Pao$_2$ and F_IO_2 were continuously recorded during the study. The first 9 babies were monitored during alternate 4- to 6-hour periods and the final 3 babies on random 4-hourly periods on servo-control or on manual control by the nurse, who adjusted the F_IO_2 if necessary. Oxygen was given according to clinical indications, by headbox or face mask or by endotracheal tube during the application of continuous positive airway pressure (CPAP) or during intermittent positive pressure ventilation (IPPV). The number of occasions during which the Pao$_2$ was outside the set limits and the duration of each occasion was calculated for each control period for different methods of oxygen administration to each baby. Paired *t* tests were used to determine the significance of differences between servo- and manual-control periods.

Results

The percentage of time spent outside the set limits of Pao$_2$ for each method of oxygen administration during servo-control and manual-control periods, is shown in the Table. The overall difference between servo-control and manual-control periods was highly significant ($t = 6{\cdot}36$; $P<0{\cdot}001$). The proportion of time during which Pao$_2$ was *below* the lower set limit was also significantly less on servo-control than on manual-control ($t = 4{\cdot}48$; $P<0{\cdot}001$). However, there was no significant difference between servo- and manual-control periods when the percentage of time *above* the upper set limits was compared ($t = 1{\cdot}87$; $P = 0{\cdot}08$).

In 11 of 12 babies the percentage of time outside the limits was less with the servo-control; in the 12th baby, the percentage was equal. Overall the Pao$_2$ was outside the set limits for 12·2% of the time when on servo-control and for 27·6% of the time when on manual-control.

The number of episodes during which the Pao$_2$ was <7·3 kPa and >10·7 kPa in the respective periods is also shown in the Table. The Pao$_2$ was below the set range on 263 occasions on servo-control and on 267 occasions on manual-control, and was above the upper set limit on 236 and 178 occasions respectively.

The mean duration of each episode *below* the lower limit on servo-control was 2·5 min and on manual-control it was 6·1 min. For the 12 patients, the difference in mean duration was highly significant ($t = 6{\cdot}51$; $P = <0{\cdot}001$). The mean duration of each episode *above* the upper limit on servo-

Table *Comparison of servo-control and manual-control periods*

Method of oxygen administration	*No. of infants**	*Control type*	*Duration (hours)*	*Percentage of time outside set limits*			*No. of episodes outside limits*		*Mean duration of episodes outside limits (min)*	
				Low	*High*	*Overall*	*Low*	*High*	*Low*	*High*
Intermittent positive pressure ventilation	5	Servo	74	8·2	6·4	14·6	145	147	2·5	1·9
		Manual	76·5	17·7	11·2	28·9	126	107	6·5	4·8
Continuous positive airway pressure	3	Servo	18	8·2	4·2	12·4	40	40	2·2	1·1
		Manual	18	23·3	6·1	29·4	42	22	6·0	3·0
Headbox	6	Servo	53	6·4	2·6	9·0	78	49	2·6	1·7
		Manual	54·5	17·3	7·8	25·1	99	49	5·7	5·2
Overall	12	Servo	145	7·5	4·7	12·2	263	236	2·5	1·7
		Manual	149	18·3	9·3	27·6	267	178	6·1	4·7

*Two babies were studied using more than one method of oxygen therapy.

control was 1·7 min and on manual-control it was 4·7 min. The difference in mean duration was significant for the 12 patients ($t = 3 \cdot 85$; $P = 0 \cdot 002$).

Discussion

This study shows that the servo-control of arterial Po_2 is not only possible, but may also improve the stability of Pao_2 in the newborn. The equipment has been used successfully to control the administration of oxygen by IPPV, CPAP, or headbox so that long periods of hypoxia or hyperoxia could be prevented.

The whole servo-control system obviously relies on the accuracy of the continuous-reading Pao_2 electrode. So far, we have relied on umbilical arterial electrodes and we find that these give a satisfactory reading for a number of days, especially when flushed continuously at a low rate. There appears to be no reason why the system should not be used with a transcutaneous oxygen electrode. This would be particularly useful in the management of apnoea in preterm babies who often require a small increase in ambient oxygen, but who are particularly prone to episodes of hyperoxia with the attendant danger of retrolental fibroplasia. Whichever sensor is used, the need for regular, formal blood-gas analysis remains.

The range of Pao_2 which we selected was 7·3–10·7 kPa. The equipment had a 1-min sampling interval and produced 5% changes in fractional inspired oxygen concentration. 10% steps were used during initial trials, but wide swings in Pao_2 occurred. Neither the optimum sampling interval nor the size of stepwise changes in F_IO_2 has been determined. The fact that the number of episodes during which the Pao_2 was above the set limits was more on servo-control than on manual-control, suggests that there may be room for improvement. Work is in progress to determine the optimum characteristics of the system for different methods of oxygen administration and for different clinical conditions.

We feel that the apparatus has a useful role to play in the management of preterm infants with respiratory problems, avoiding the necessity for constant observation of a Pao_2 monitor and frequent manual adjustments of the fractional inspired oxygen concentration. The relative stability of Pao_2 achieved by the servo-control equipment seems certain to contribute to a reduction in morbidity in sick newborn babies.

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Structural heart disease in the newborn

Changing profile: comparison of 1975 with 1965

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SUMMARY The earlier detection and investigation of babies with congenital structural heart disease has resulted in earlier treatment and better management of these patients. In 1965, at the Hospital for Sick Children, Toronto, 121 cases were assessed and treated; by 1975 this figures had risen to 226 cases. Few changes were noted in the incidence of the 10 most common malformations, except for the obvious increase in the incidence of patent ductus arteriosus due to survival of increasingly premature infants. The sick cardiac neonate was referred earlier in 1975, studied with newer non-invasive investigations, and, according to the severity of symptoms and signs, was sent sooner to cardiac catheterisation. 80% of babies presenting with cyanosis survived the first month and 60% of babies with congestive heart failure survived. With better surgery and perioperative care, the survival rate in the first month after surgery rose from 37% in 1965 to 70% in 1975.

During the last decade there has been a wider recognition of the need for early referral and aggressive management of the newborn with cardiac malformation (Fyler, 1968; Varghese *et al.*, 1969). The increasing complexity of diagnostic procedures and support services, and the use of specialised surgical techniques (Mustard *et al.*, 1970; Edmunds *et al.*, 1972; Barratt-Boyes *et al.*, 1973), have resulted in a trend to regionalise these efforts (Fyler *et al.*, 1972; Nadas *et al.*, 1973; D. Cook *et al.*, 1978, unpublished data). Consequently, the numbers of patients admitted for this type of care have increased. This hospital reported that 211 neonates with congenital heart disease were assessed retrospectively for the period 1953–57 (Rowe and Cleary, 1960). By 1965, 121 neonates with heart malformation were being seen yearly.

In this paper the presenting features, type of anomaly, investigative techniques, and results of treatment in newborn patients with heart malformations seen in 1965 are compared with a prospective group of 226 such babies seen in 1975.

Materials and methods

Newborn infants seen with congenital heart malformations at this hospital in 1965 were analysed retrospectively by searching our data bank for infants with cardiac malformations; this data bank has been in operation since 1952 (Rose *et al.*, 1972).

Patients seen in 1975 were evaluated prospectively as neonates requiring cardiological consultation at the hospital. The newborn was first seen by a fellow in cardiology and shortly afterwards by a staff cardiologist. Preliminary investigations, apart from a physical examination, included blood-gas measurements, a chest *x*-ray, and an electrocardiogram. Echocardiograms were obtained in 128 of the 226 patients with structural heart disease. Results of the preliminary investigations and the recommended treatments were communicated to the appropriate unit staff. Further investigation by cardiac catheterisation and angiocardiography was performed after such consultations in 117 patients. Subsequent evaluations on the ward were performed by cardiologists usually daily, but more or less often according

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to need. Follow-up after discharge, arranged through the referring physician, depended on the severity of the residual cardiac anomaly and the likelihood of future problems.

The final diagnosis was established at necropsy, surgery, cardiac catheterisation, or by clinical assessment only, in descending order of certainty. If multiple defects existed, the most important malformation was listed. A few broad categories of diagnosis were used. For example, hypoplastic left heart syndrome included aortic valve atresia, mitral valve atresia, and hypoplasia of all left heart structures without atresia. In the group hypoplastic right heart syndromes were lesions with hypoplasia of the right ventricle, particularly pulmonary atresia with intact ventricular septum and tricuspid valve atresia.

Premature infants with patent ductus arteriosus (PDA) were included in the group with structural heart disease because they were assessed according to their need for pharmacological or surgical treatment, as was the case with the other structural cardiac defects seen during 1975.

A second group of neonates with nonstructural heart disease are reported separately (Rowe *et al.*, 1978).

Results

Table 1 summarises the final diagnoses in the neonates with structural congenital heart disease. The 10 most common defects are listed in order of frequency in 1975 and compared with the prevalence in 1965. The obvious change between the two years is the pronounced increase in the number of PDA in 1975. Although the absolute number of patients with D-transposition of the great arteries (complete transposition of the great arteries) rose by half, from 18 to 27, this malformation was still in second place in 1975.

Table 1 *Incidence of common structural cardiac defects in neonates in 1965 and 1975*

Final diagnosis	*1965 (n=121)*		*1975 (n=226)*	
	No.	*%*	*No.*	*%*
Patent ductus arteriosus	10	8	69	31
D-transposition of the great arteries (complete transposition)	18	15	27	12
Hypoplastic left heart syndrome	11	9	21	9
Ventricular septal defect	19	16	25	11
Coarctation of aorta syndrome	10	8	16	7
Hypoplastic right heart syndrome	7	6	8	4
Tetralogy of Fallot	10	8	9	4
Aortic valve stenosis	1	1	5	2
Dextrocardia	8	7	6	3
Pulmonary valve stenosis	3	2	6	3
Others	24	20	34	15

The sex ratio in both groups shows there were more boys than girls, but this trend is diminishing (Table 2). A significant reduction in the birthweight of the neonate with structural heart disease seen in 1975 is apparent (Table 2). In 1975, the mean age at first assessment was 6·8 days compared with 8·3 days in 1965 (Table 2). If the patients with PDA as the principal defect are excluded, the mean age at first assessment in 1975 was 5·4 days. The patients with PDA were mainly premature infants who did not show evidence of the shunt until the second week of life.

A greater reduction is noted in the interval from initial clinical assessment to cardiac catheterisation between 1965 (5·3 days) and 1975 (1·8 days) in Table 3. The two main indications for cardiac catheterisation in the neonate are central cyanosis and congestive heart failure (Rowe, 1970). With increasing severity of these indications, there is a greater urgency to proceed to cardiac catheterisation. This urgency is reflected in the shorter time interval to cardiac catheterisation in 1975 compared with 1965 (Table 4).

Table 2 *Clinical data of neonates with structural cardiac defects assessed in 1965 and 1975*

Year	*No.*	*Sex ratio F/M*	*Birthweight (kg)*		*Age at first assessment (days)*	
			Mean	*SD*	*Mean*	*SD*
1965	121	0·76	3·1	0·7	8·3	7·1
1975	226	0·84	2·8	1·0	6·8	2·2
			$t = 3{\cdot}26$ $P<0{\cdot}005$		$t = 2{\cdot}26$ $P<0{\cdot}025$	

Table 3 *Interval from initial clinical assessment to cardiac catheterisation in neonates with structural heart disease, 1965 and 1975*

Year	*Mean interval (days)*	*No.*
1965	5·3	66
1975	1·8	117
		$P<0{\cdot}001$

Table 4 *The influence of cyanosis and congestive heart failure on the interval from initial clinical assessment to catheterisation, 1965 and 1975*

Year	*Cyanosis*			*Heart failure (mean, days)*		
	Mild	*Moderate*	*Severe*	*Mild*	*Moderate*	*Severe*
1965	7·4	3·4	3·1	4·8	5·9	3·5
1975	1·3	0·2	0·2	4·3	2·6	0·3
	$P<0{\cdot}001$	$P<0{\cdot}001$	$P<0{\cdot}01$	NS	$P<0{\cdot}025$	NS

NS = not significant at conventional (5%) level.

Approximately one-half of patients with structural heart disease were admitted for noncardiac reasons, the majority being premature infants with PDA who initially were admitted for prematurity alone or with respiratory distress, jaundice, or hypoglycaemia. The remaining patients, who were admitted with suspected cardiac malformations, showed cyanosis or congestive heart failure. The severity of the defects was not based on the presence or absence of heart failure or cyanosis, but rather on the basis of the patient undergoing cardiac catheterisation, surgery, or dying, as was done in the New England series (Fyler *et al.*, 1972). The survival rates of babies with or without cyanosis and/or congestive heart failure were higher in 1975 than in 1965. Statistically, the higher survival rate in patients with congestive heart failure was not significant (Table 5). The presence or absence of the patients with PDA in the category with cyanosis and/or congestive heart failure had little effect as the survival rate was greater in 1975 than in 1965 (Table 6).

The assessment of the acid-base status of the 10 groups is best appreciated by their division into three physiological groups as in Table 7, the first with central cyanosis or hypoxaemia, the second with pressure load, and the third with volume load. Examination of blood pH shows that acidosis occurs in all severe cases, but not necessarily in the mild. Acidosis is more severe in left heart obstruction with impaired peripheral perfusion (pH = 7·23). The highest value of Pco$_2$, hypercapnia, was in the volume load group (45 mmHg) and the lowest, hypocapnia, in the left heart obstruction group (25·2 mmHg). As expected, the maximum drop in Po$_2$ was in the hypoxaemia group (23·0 mmHg in D-transposition of the great arteries). The hyperoxic test indicates little rise in Po$_2$ in the hypoaemic group (23·0 to 24·7 mmHg mean).

In 1975, of 53 neonates undergoing cardiac surgery there were 37 (70%) survivors compared with a rate of 37% (13 of 35) in 1965 (Table 8). This increase in survivors undergoing surgery within the month in 1975 compared with 1965, was not due to increase in ligation of PDA. Despite the increase in this lesion, the number of ligations in 1975 in the first month of life was 5 with 4 surviving and 1 in 1965 who survived. The survival with Blalock-Hanlon procedure in D-transposition of the great arteries (complete transposition), was much improved in 1975. 16 neonates underwent this procedure under one month without a death in 1975; only 3 of 12 survived in 1965. The results with this operation accounted for part of the major improvement.

Table 6 *Survival of neonates with congenital structural heart defects (including and excluding patients with patent ductus arteriosus) and central cyanosis, congestive heart failure, or both, 1965 and 1975*

Year	*With PDA*		*Without PDA*	
	Survivors	*Total*	*Survivors*	*Total*
1975	83 (62·9%)	132	70 (60·9%)	115
1965	33 (37·9%)	87	32 (37·6%)	85
	χ^2 = 11·35 P<0·001		χ^2 = 9·63 P<0·005	

Table 7 *Arterial blood–gases measured in categories of congenital structural heart disease in the neonate, 1975*

	pH	*P*co$_2$ (*mmHg*)	*P*o$_2$ (*mmHg*)	*Hyperoxic P*o$_2$ (*mmHg*)
Hypoxaemia				
Severe (TGA)	7·30	36·9	23·0	24·7
Mild (T/F)	7·38	29·8	39·3	42·7
Pressure load				
Severe (HLH)	7·23	25·2	52·5	—
Mild (Co Ao)	7·25	39·7	59·9	—
Volume load				
Severe (Talner, 1970)*	7·35	45·0	56·0	—
Mild (VSD)	7·38	33·6	63·5	—

TGA = Transposition of great arteries; T/F = Tetralogy of Fallot; HLH = Hypoplastic left heart; Co Ao = Coarctation of aorta; VSD = Ventricular septal defect.

*29 volume loaded hearts in infants who were critically ill. 16 out of 29 had large ventricular communications.

Conversion: traditional units to SI—Pco$_2$ and Po$_2$: 1 mmHg ≈ 0·133 kPa.

Table 8 *Survival at least one month after surgery in congenital structural heart disease in the neonate, 1965 and 1975*

Year	*Total no.*	*Survival >1 month*	
		No.	*%*
1965	35	13	37·1
1975	53	37	69·8

χ^2 = 9·17
P<0·005

Table 5 *Survival of neonates with congenital structural heart defects and central cyanosis, congestive heart failure, or both, 1965 and 1975*

Year	*Cyanosis*			*Congestive heart failure*			*Combined cyanosis and congestive heart failure*			
	Survived	*Died*	*Total*	*Survived*	*Died*	*Total*	*Survived*	*Died*	*Total*	*Grand total*
1975	45 (80·4%)	11	56	22 (59·5%)	15	37	16 (41%)	23	39	132
1965	21 (55·3%)	17	38	9 (39·1%)	14	23	3 (11·5%)	23	26	87
	χ^2 = 5·66 P<0·025			χ^2 = 1·60 NS			χ^2 = 5·20 P<0·025			

With medical treatment only, including patients with PDA, the survival rate in 1965 was 61% (54 out of 89) and in 1975 it was 75% (128 out of 170) ($\chi^2 = 5 \cdot 3$). If the patients with PDA are excluded, the survival rate was 58% (46 out of 80) in 1965 and 67% (72 out of 107) ($\chi^2 = 1 \cdot 8$) in 1975. The survival rate is higher in 1975 than in 1965, even with the PDA cases excluded, but the difference is not significant because of the smaller number of cases.

The management and prognosis of the neonate with heart disease may be influenced by the presence of extracardiac anomalies (Greenwood *et al.*, 1975). 26% of neonates with structural heart disease in 1975 had anomalies of systems other than the cardiovascular system. In 20% (45 out of 226) of the patients, admission was initiated because of the extracardiac anomalies. Mortality may have been influenced by the extracardiac anomalies in 28% (16 out of 57) with these additional defects.

Discussion

In 1960, the first report on congenital heart disease in the newborn from Toronto estimated the probable number of fatal cases there from the cases examined at the Hospital for Sick Children before death in the preceding 5 years. Fewer than half of these cases reached the hospital before death (Rowe and Cleary, 1960). In that period, 149 newborn babies with signs of heart disease survived the first month. The emphasis was on the difficulty of finding cases of congenital heart disease early and the need to separate severe from the less severe malformations. This was the preliminary to improving the survival of the seriously affected cases.

By 1965 the annual case load of structural heart disease was 121 patients. There were 13 survivors over a month postoperatively of 35 undergoing surgery in the neonatal period, a survival rate of 37%.

For comparison, a Buffalo survey for the period 1949–64, reported a survival rate of 31% (10 out of 32) in this age group (Lambert *et al.*, 1966). The figure from New Zealand for 1969–71 was 50% (6 out of 12) survival (Barratt-Boyes *et al.*, 1972).

Towards the latter part of the decade cardiac catheterisation was being widely used because of the improvement in mortality from heart disease at this age (Fyler, 1968, 1969; Varghese *et al.*, 1969). For example, the procedure of balloon atrial septostomy during cardiac catheterisation introduced in this period greatly accelerated the improvement in the survival rate of D-transposition of the great arteries. Surgical techniques suited to the smaller infant also became applicable (Mustard *et al.*, 1970; Edmunds *et al.*, 1972; Barratt-Boyes *et al.*, 1973).

The recognised need to improve case finding and facilitate treatment was first appreciated by the New England Regional Infant Cardiac Program in 1969 (Fyler *et al.*, 1972) and within 4 years the case study within that programme had been shown to be complete (Nadas *et al.*, 1973).

At the turn of the decade, the Study Group of Congenital Heart Disease of the Intersociety Commission for Heart Disease Resources was recommending a stratified system to promote optimal care for all ages (Engle, 1972).

With better understanding of the biological changes occurring in hypoxia and congestive heart failure in the newborn with serious heart disease, management of these changes pre- and postoperatively improved and aided in the survival of the patients (Rowe, 1970; Talner and Ithuralde, 1970; Gersony and Hayes, 1972; Talner and Campbell, 1972).

In an attempt to evaluate the impact of these changes, we have reported here our experience for 1975 and compared it with that for 1965. The number of referrals and patients with structural heart disease (226) seen in one year, was equal to the total seen in the 5 years before the 1960 report. A few changes were noted in the incidence of various malformations. The obvious increase in the incidence of PDA is related to the survival of increasingly more premature infants in whom the incidence of PDA is rising (Siassi *et al.*, 1976).

The sick cardiac patient in 1975 was referred and seen earlier than in 1965. Before cardiac catheterisation, a number of newer noninvasive assessments helped to plan invasive investigations and decreased the time and improved the quality. Such assessment included the use of blood–gases to determine the acid-base status, the hyperoxic test for cyanotic patients, and echocardiography (Rowe, 1970; Talner and Ithuralde, 1970; Godman *et al.*, 1974; Hagler, 1976; Meyer, 1977; Williams and Tucker, 1977). The interval from first assessment to cardiac catheterisation decreased with greater severity of cyanosis or congestive heart failure, reflecting the trend towards earlier and more complete investigations.

With the more aggressive and newer approach to investigation, the prognosis with treatment is improving. In 1965, 61% of neonates were surviving one month after medical treatment, but by 1975 the figure was 75% ($0 \cdot 02 < P < 0 \cdot 025$). A number of factors influence the result of medical treatment. If the patients with PDA are excluded, the survival rate with medical treatment was 58% in 1965 and 67% in 1975 ($\chi^2 = 1 \cdot 8$); the difference is not significant because of the smaller number of cases, particularly in 1975. Some patients will be treated medically because the lesion may be inoperable, as with aortic valve atresia, while others will have quite minor defects and transient disturbances which respond well to medical treatment.

With improved surgery and perioperative care, the survival rate in the first month after surgery rose from 37% in 1965 to 70% in 1975 ($P<0\cdot005$).

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Seroepidemiology of cytomegalovirus infections during the first years of life in urban communities

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SUMMARY Using indirect haemagglutination assay, combined with a collection of blood samples on blotting cards, seroepidemiological surveys of cytomegalovirus infections during early infancy have been done in different populations (French and immigrant) in urban areas. The comparison of CMV antibody status of mothers and their children at 10 months and at 2 years of age enables possible factors of viral transmission to be defined. During the first year of life, seropositive mothers were the only source of infection and they remained the main source during the second year. Socioeconomic class and educational level are determinant factors in the incidence of viral transmission.

There are wide variations in the incidence of infection by cytomegalovirus (CMV) in infants, related to socioeconomic classes and ethnic groups (Lang, 1975; Hanshaw, 1976). Epidemiological analysis of these variations is needed but this requires large surveys in different populations. This has been difficult because virus isolations cannot be used in large surveys, and serological tests have been made mainly by complement fixation (CF), a test having variable sensitivity; some CF-negative subjects had detectable CMV specific antibodies when more sensitive techniques (immunofluorescence, platelet-agglutination) were used (Weller, 1971; Stagno *et al.*, 1975).

The indirect haemagglutination (IHA) assay (Fucillo *et al.*, 1971; Huraux *et al.*, 1971) is a sensitive and specific technique for detecting CMV antibody and it can be used on a large scale for seroepidemiological surveys, especially when it is combined with the collection of blood samples on blotting cards requiring only a few drops of blood (Cabau *et al.*, 1976). We used this technique in a seroepidemiological study of CMV infections on infants during the first two years of life in different urban populations.

Subjects and methods

This study was carried out at two public health centres where children are seen for health check-ups at ages 10 months, 2 years, and 4 years. Children and their mothers spend between 3 and 4 hours in the centre during which time the child has a complete medical examination and some laboratory tests, and the mother has a psychological interview. The first centre (centre A) is in Clichy, a suburb north of Paris in which socioeconomic conditions are generally low and housing facilities poor. The second (centre B) is in the 13th district of Paris (south); a large part of it has recently been rebuilt with modern apartments, and it is inhabited mainly by the middle class. In both centres about 80% of people are French, the others are immigrants mainly from Africa, Spain, or Portugal. A blood sample was taken from the finger of mother and child, and sometimes from the father, filling the three circles of the blotting cards for a PKU test.

Information about the socioeconomic conditions of the families was obtained and clinical investigations were made by nurses and paediatricians not connected with the study. Once a week the cards were posted to the laboratory.

Serology. On arrival at the laboratory the cards were stored at 4°C. Serum was eluted from the dried blood specimens collected on the three circles in 1 ml buffer, giving a dilution of about 1:10 of the serum.

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Serum was eluted within two weeks of taking the blood specimen. IHA assays were used for CMV antibody with the AD-169 strain of CMV as source of antigen, using the technique of Fucillo *et al.* (1971) modified by Cabau *et al.* (1976). Each sample was titrated from 1:10 up to 1:5120; mothers with an antibody titre < 1:10 and 10-month-old children with an antibody titre < 1:40 were considered negative. A previous longitudinal serological study had shown that in some infants born to CMV antibody-positive mothers, maternally-transmitted CMV antibodies could still be detected at 10 months by IHA assay, but the titres were < 1:40 (Cabau *et al.*, 1977). After a primary CMV infection proved by the presence of CMV antibody in IgM fractions, antibody titres were >1:40 at 10 months in every case; so in this study any infant with a CMV antibody titre >1:40 was presumed to be infected. It is not possible to establish if some of these infections were acquired *in utero.*

Results

CMV antibody studies in mothers and their 10-month-old children. 229 mothers and their children were tested at centre A and 399 at centre B (Table 1). At centre A, 71·6% of the mothers had CMV antibody compared with 56% at centre B. In the French mothers, 66·5% of them gave seropositive results at centre A compared with only 47·4% at centre B. At both centres a high percentage (about 90%) of immigrant mothers had CMV antibodies.

Comparison of CMV antibody in the 10-month-old infants shows striking differences: in centre A, 28·4% were seropositive; in centre B, 10%. Among French children 25·8% were seropositive in centre A, and 5·1% in centre B. A small difference was noted among immigrant children: 38% in centre A, 27% in centre B.

Table 1 *CMV antibody status of mothers and 10-month old children*

Centre	*Population*		*CMV antibody status*	
	Ethnic groups	*No.*	*Positive mothers*	*Positive children*
			No. (%)	*No. (%)*
A	French	182 (79·5%)	121 (66·5)	47 (25·8)
	Immigrant			
	African	27	26 (96)	10 (38)
	Spanish–Portuguese	16	14 (87)	5 (35)
	Others	4	3	3
	Total	229	164 (71·6)	65 (28·4)
B	French	310 (77·7%)	147 (47·4)	16 (5·1)
	Immigrant			
	African	45	37 (82)	11 (24)
	Spanish–Portuguese	16	15 (94)	3 (19)
	Others	28	25 (89)	10 (35)
	Total	399	224 (56)	40 (10)

All 10-month-old infants who were seropositive had seropositive mothers, while none of the seronegative mothers had a seropositive child. Among seropositive mothers, in centre A 47 (39%) of 121 French mothers and 18 (42%) of 43 immigrant mothers had a seropositive child: in centre B 16 (11%) of 147 French mothers, and 24 (31%) of 77 immigrant mothers had a seropositive child. The serological titres of mothers were not related to the fact of whether or not their children were seropositive.

Some factors which may affect the transmission of virus from mother to infant were studied. There were no differences in the proportion of children delivered by caesarean section, nor were there differences in the proportion of children who attended day nurseries during the first months of life.

The proportion of children who were breast fed by seropositive mothers was studied in relation to the antibody status of the child at 10 months of age (Table 2). When results of the two centres were combined, significant differences (but only at the 5% level) were found between seropositive children (29% were breast fed < 8 weeks and 23% >8 weeks) and seronegative children (20% < 8 weeks and 15% >8 weeks).

At both centres certain socioeconomic factors (housing, education) were correlated with CMV antibody status of the mother and the child. In centre A there were no differences as all these people were in lower socioeconomic classes. In centre B some significant differences emerged: if both mother

Table 2 *Antibody status of the child related to breast feeding*

	Centre	*Mother+ Child+*	*Mother+ Child−*	*Significance of difference*	*Mother− Child−*
Breast feeding < 8 weeks	A	27/99	14/65	NS	16/61
	B	15/46	34/178	S	38/178
	Total	42/145 (29%)	48/243 (20%)	S	54/239 (23%)
Breast feeding >8 weeks	A	23/99	7/65	S	10/61
	B	11/46	29/178	NS	23/178
	Total	34/145 (23%)	36/243 (15%)	S	33/239 (14%)

NS = Difference between the groups mother+child+, mother+child− is not significant; S = significant at 5% level between the groups: mother+ child+, and mother+child−.

Table 3 *Socioeconomic conditions in centre B families*

Criteria		*CMV antibody status*		
		Mother+ Child+	*Mother+ Child−*	*Mother− Child−*
Families with good housing standards (%)		39	46	59
Fathers with only elementary education	Total	27	12	13
	French	35	9	8·7

and child were seropositive their socioeconomic conditions tended to be low (Table 3).

The educational level of the fathers was compared. In French families, for which information was more reliable, in cases where both mother and child were seropositive, only 35% of fathers had had elementary education alone, compared with 9% of fathers in the other two groups.

Development of CMV antibodies in children at 10 months and 2 years and in their mothers. At centre B we collected blood samples from 262 mothers and their children at a second check-up examination at 2 years of age. Table 4 shows correlations between the results for each mother and child according to the antibody status of the 1st and 2nd samples. In 247 (94·3%), no change was observed in the CMV antibody status of mother and child. Nine CMV seronegative 10-month-old children with seropositive mothers became seropositive at 2 years of age. Two CMV negative 10-month-old children became seropositive but their mothers remained seronegative. Four seronegative mothers became seropositive and, in two instances, the child also became seropositive.

Differences were found between the French and immigrant families. In the 224 French families, 13 (6%) had a seropositive child at 10 months and 20 (9%) at 2 years. If the French seropositive mothers are considered, 13 (13%) out of 97 had a 10-month-old seropositive child and 18 (18%) out of 100 a seropositive child at 2 years. In the 38 immigrant families 12 (31%) had a seropositive child at 10 months and 18 (47%) at 2 years. In the group of seropositive mothers the figures are respectively 12 (34%) out of 35 and 18 (50%) out of 36.

Among factors which may indicate a possible source of CMV infection we noticed that in the 9 children who had seropositive mothers at 10 months and who became seropositive at 2 years, 6 stayed in day nurseries and 3 were nursed at home by their mothers. The 2 children who became seropositive with their mothers still seronegative, and the 2 children who seroconverted, as did their mothers, attended day nurseries from age 4–5 months. In the two observations in which the mothers became positive, only in the 2nd sample was the child nursed by the mother.

As a result of the clinical examination of the infants at 10 months and at 2 years, nothing of note was detected in those children with CMV antibodies.

Discussion

The use of IHA assays of blood samples collected on blotting cards is practical for surveys such as this. Samples may be posted, as an earlier study (Cabau *et al.*, 1976) showed that if elution is done within 2 weeks, correlation with titres using conventional serum samples is good. Even in specimens with low titres, no false-negatives were found. The method is useful for large surveys, and is accepted readily by the population (especially in infants from whom it is easy to obtain a few drops of blood) and by the doctors and nurses who collect the samples.

The presence of CMV antibodies in a mother at the time of the visit of her 10-month-old child probably reflects her antibody status at pregnancy. Of the 262 women who were tested twice at an interval of 14 months, only 4 showed seroconversion. Of the mothers who were seropositive in both tests, none showed significant change in titre. This stability of CMV antibody titre using IHA assay contrasts with fluctuations of CF antibody titre (Waner and Weller, 1973).

In this study the presence of CMV antibody after a primary infection in the child could clearly be seen to relate to the presence of CMV antibody in the mother, consistent with earlier reports (Levinsohn *et al.*, 1969; Andersen *et al.*, 1972; Leinikki *et al.*, 1972; Granström *et al.*, 1977).

Intrapartum contact with infected cervical secretions has been supposed to be the main cause of these

Table 4 *CMV antibody status of mothers (M) and their children (C) at 10 months and 2 years of age*

	CMV antibody status						
	No change			*Change*			
10 months	M+C+	M+C−	M−C−	M+C−	M−C−	M−C−	M−C−
2 years	M+C+	M+C−	M−C−	M+C+	M+C−	M+C+	M−C+
French	13	80	122	4	2	1	2
Immigrant	12	18	2	5	0	1	0
Total	25	98	124	9	2	2	2

early infections. A longitudinal study on some children without specific IgM antibody at birth, but in whom CMV antibody was present at one year, showed that they had all acquired detectable specific IgM antibody between 3 and 6 months of age, suggesting early contamination, probably an intrapartum viral transmission (Cabau *et al.*, 1977). The fact that the incidence of caesarean sections did not vary in the different groups may be due to the fact that it was not possible to determine whether caesarean sections were before or after membrane rupture.

The percentage of children who were breast fed is significantly higher (but only at 5% level) in the group of children who had a primary CMV infection. When these results are correlated with socioeconomic criteria (e.g. parents with primary educational standard only) the difference remains. The high frequency of breast feeding is not related to low socioeconomic conditions, in agreement with general observations in French urban populations.

Consideration of the 13 children who showed CMV seroconversion between 10 months and 2 years supports the idea that mothers are the most important source of infection (9/13). Other sources may exist; for instance, both children who acquired CMV antibodies while their mothers remained negative attended nurseries. In the 2 cases where mothers and children both became CMV seropositive, the children also attended day nurseries and it is not known whether the mother or the child was first infected.

We conclude that during the first year of life mothers constitute the main, if not the only, source of CMV infection, and they remain the most common source of infection during the 2nd year of life also. In seropositive mothers CMV has been isolated in cervical secretions and in milk (Hayes *et al.*, 1972), and CMV infection is also considered a 'kissing disease'. During the 2nd year of life some extra-maternal sources of infection appear. Close contact between children in day nurseries is a possible mode of spread, but seems rare: 47% of seronegative children with seronegative mothers attended day nurseries, but no more than 4 children were infected by CMV.

This survey also demonstrates the importance of socioeconomic conditions in the transmission of CMV infections during the first 2 years of life. The incidence of infection depends on two factors: (1) the percentage of seropositive mothers, the potential source of virus, and (2) the percentage of infection of children from seropositive mothers.

In our groups of differing socioeconomic class, the percentage of seropositive mothers differed (centre A 66·5%; centre B 47·4%) as did the frequency of infection in their children (centre A 38·8%; centre B 10·8%). These two factors result in figures of 5 to 25% for the acquisition of seropositivity by 10 months in the two groups. In other surveys on French infants we have found a figure of 5% in a rural group and 76% in a poor urban group (Boué *et al.*, 1976, and unpublished).

In immigrant groups, the percentage of seropositive mothers was about 90%. They were infected mainly in their native country, but a slight difference is shown in the percentage of their seropositive children (centre A 41·8%; centre B 31·1%). In a previous study of very poor immigrant families living in Paris suburbs, 90% of the infants were seropositive (Boué *et al.*, 1976), a high frequency of early acquisition of antibody and similar to that observed in African populations (Lang, 1975; Cabau *et al.*, 1977). The improvement in living and educational standards of immigrant families reduces the frequency of early infection. It is of note that in centre A where the standard of living was similar in both French and immigrant groups, the percentages of seropositive children born from seropositive mothers were also very similar. In contrast with the above figures, only about 5% of 'middle-class' 10-month-old children have CMV antibodies.

These facts underline the importance of the standard of living in determining the transmission rates of CMV infections from mothers to infants. Not only are economic conditions (housing, income of the family) relevant, but so also are the prevailing hygiene habits, and these can be influenced by education.

We have found that the use of IHA assays of blood collected on blotting cards provides a practical tool for large surveys. What is needed is to follow-up pregnant women and their babies in different population groups, and then measure the incidence of intrauterine infections and their relation to living standards and personal hygiene. Such studies are indispensable if policies leading to prevention are to be formulated.

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The spread of Coxsackie B1 infection

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SUMMARY During June and July 1977 5 junior boys in a boarding school for 800 pupils became ill with a mild infection caused by Coxsackie B1. The school had been taking part in a vaccine trial, and paired blood samples had been taken from new entrants in October 1976 and October 1977. 18% of the boys susceptible to the infection developed antibodies. The results suggest that dormitories are more important than the day-to-day contacts in the spread of infection. The advisability of nursing children with known or suspected enterovirus infections in open wards in hospital is questioned.

The interfamilial and institutional spread of Coxsackie B2 and B5 viruses has been well documented (Carmichael *et al.*, 1968; Broughton and Gostling, 1969; Lapinleimu and Kaski, 1972; Eilard *et al.*, 1974), but there have been few accounts of Coxsackie B1 (Yodfat and Nishmi, 1973). *Communicable Disease Reports* (Public Health Laboratory Service, 1964–1977) show that since 1967 there have been two small outbreaks in England and Wales, the first began in 1970 and the second in 1976 (Figure). Each lasted two years, the distribution of cases being biphasic, peaking in the summer months.

Christ's Hospital is a boarding school for 800 pupils aged between 11 and 19 years. The younger boys live in six houses. They are in forms for teaching, and then are split into sets for mathematics, French, Latin, etc., which are constituted differently from forms, and all the boys use a central dining hall. The range of contacts during the day must, therefore, be large. During June and July 1977, 5 junior boys became ill with a mild infection caused by Coxsackie B1. The school had been taking part in a trial of inactivated influenza vaccine (Hoskins *et al.*, 1976), and paired blood samples had been taken in October 1976 and October 1977 from 124 new entrants. This paper describes the spread of the infection.

Methods

Virus isolation. Throat swabs were collected into transport medium at the onset of illness. In the laboratory the specimens were inoculated into primary rhesus monkey kidney, human embryonic lung fibroblast, and Hela cell tissue cultures. These were incubated, rolled at 35°C for 15 days, and examined daily for cytopathic effect. Coxsackie B1 isolates were identified by neutralisation tests on the tissue culture fluids.

Neutralisation tests. Blood samples were collected in October 1976 and October 1977, the sera were stored at − 20°C until tested. Serum neutralisation tests were carried out in flat-bottomed microtitre trays using $0\cdot05$ cm^3 unit volumes. Serum dilutions were prepared in the trays and 1 unit volume of Coxsackie B1 virus was added to each serum dilution. After mixing, trays were left at room temperature for one hour, when 1 unit volume of a suspension of Vero cells was added to each well. Trays were incubated in a moist chamber for 3 days at 35°C. Presence of specific antibody was judged by inhibition of cytopathic effect. Sera with titres < one in 20 were recorded as 'without antibody'.

Results

Clinical findings. The 5 boys were aged between 12 and 13 years. All complained of headaches and

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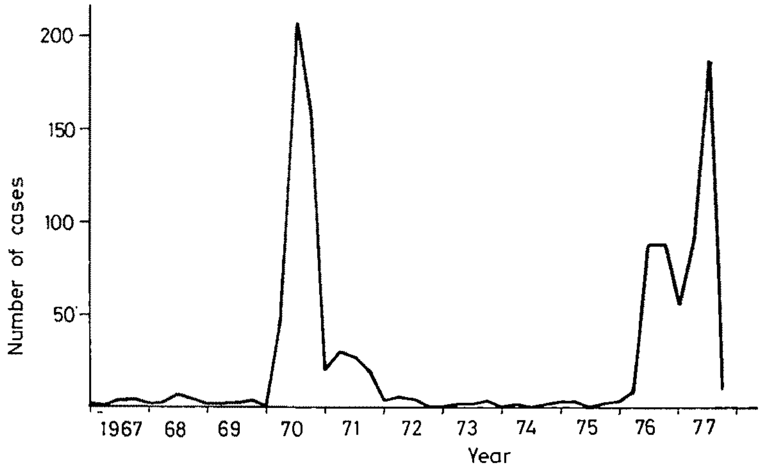

Figure *Number of cases in which Coxsackie B1 was isolated during the years 1967–77 (from the Communicable Disease Reports of the Public Health Laboratory Service).*

sore throats, and 4 of them had fevers of >38·3°C. In these boys the fever lasted from 2 to 5 days and the total length of illness was 6. In 2 boys there was some injection of the fauces and, in a 3rd, slight neck stiffness. The 5th boy was not pyrexial and spent only one day in the school infirmary. Convalescence was uncomplicated and there were no sequelae.

Epidemiology. During the period 13th June–11th July 1977, throat swabs were taken from 18 boys in the junior houses. Coxsackie B1 was isolated in 5. There were no viral isolates in the remaining 13. Throat swabs were also taken from 28 boys in the senior houses, none of which showed evidence of Coxsackie B1 infection. Thus, from these results and the clinical picture, the outbreak appears to have been confined to the junior houses. 124 new entrants in October 1976 had had sera taken. 24 (19%) had Coxsackie B1 antibodies and 100 (81%) were negative. By 1977, 18 of these were positive, suggesting that 18% of the boys known to have been susceptible to the infection had developed antibodies during the previous year. These included 2 with positive throat swabs.

Spread in the classrooms

The boys from the junior houses are in three form groups—II, III, and LE. Table 1 shows that the 5 boys with positive throat swabs were in forms IIB, IIIA, B, C, and E. The results of the neutralisation tests show that, of the 124 boys who had paired sera taken in the individual classes, there does not appear to be any association between the clinically

Table 1 *Results of Coxsackie B1 neutralisation tests and isolations in throat swabs according to school form*

Form	*Throat swabs Coxsackie B1*		*New entrants 1976*			
	Isolated	*Not isolated*	*Sera taken*	*Negative 1976*	*Converted 1977*	
					No.	*% of negative*
IIA	0	0	16	11	3	27
IIB	1	0	19	16	3*	19
IIC	0	1	19	16	5	31
IID	0	0	17	11	1	9
IIE	0	2	17	13	2	15
IIIA	1	2	9	9	3*	33
IIIB	1	0	7	7	0	—
IIIC	1	1	9	7	1	14
IIID	0	0	2	2	0	—
IIIE	1	0	4	3	0	—
IIIF	0	2	5	5	0	—
IIIG	0	0	0	0	0	—
LE	0	5	0	0	—	—
Total	5	13	124	100	18	18

*Also had a positive throat swab.

confirmed cases and those with serological evidence of a subclinical infection. In forms IIB, IIIA, and IIIC, both clinical and subclinical infection occurred. In forms IIIB and IIIE, both with clinical cases, there was no evidence of seroconversion among those who had paired sera taken, whereas in forms IIA, C, D, and E where there were no clinical cases, there was serological evidence of subclinical infection.

Spread in the dormitories

Table 2 shows that the 5 ill boys with positive swabs came from two houses—Leigh Hunt A and Barnes A. Each of the six junior houses has two dormitories with about 30 boys in each. The distance between any two beds is 900 mm in accordance with *The Standards for School Premises Regulations* (Great Britain Statutory Instruments, 1972). In Leigh Hunt A one of the boys with a positive throat swab slept in the upper dormitory and the two others in the lower dormitory. In Barnes A one was in the upper and one in the lower dormitory.

The proportion of boys who had paired sera taken was similar in each house.

In Leigh Hunt A, of the 7 boys who had seroconverted, 4 slept in the upper dormitory, 3 of them in adjacent beds. The beds of the 3 in the lower dormitory were not close together.

In Leigh Hunt B, all 4 boys with a subclinical infection came from the upper dormitory. One had been sleeping in the infirmary throughout June because of nocturnal epilepsy.

In Barnes A, the 3 boys who had seroconverted slept in widely separated beds in the upper dormitory. (Paired sera had not been taken from the clinical cases.)

In Barnes B, 4 boys had evidence of a subclinical infection. One slept at home and the remaining 3 boys were in the lower dormitory and slept in adjacent beds. There was no evidence of infection in the upper dormitory.

There were no known cases, clinically or subclinically, in the four dormitories of Maine A and B, although 83% of the boys in these houses had no detectable antibody to Coxsackie B1 in October 1976.

Thus, clinical and known subclinical infection was confined to 6 of the 12 dormitories. In two houses the infection occurred in only one dormitory. Of the 18 boys with paired sera who showed evidence of infection, two groups of 3 slept in adjacent beds.

Discussion

The Coxsackie B group of viruses are associated with a broad spectrum of clinical illness, ranging from a mild febrile infection to severe encephalitis (Kibrick, 1964; Assaad and Cockburn, 1972). A fatal case due to Coxsackie B1 in a newborn baby has been reported (Wright *et al.*, 1963).

This outbreak was not serious in itself. The results suggest that the dormitories and sleeping quarters are more important than the day-to-day contacts in the spread of this infection. While this has obvious implications in boarding schools and children's homes, it also raises the question of the advisability of nursing children with known or

Table 2 *Results of Coxsackie B1 neutralisation tests and isolation in throat swabs 1976 and 1977 according to school house*

	Leigh Hunt A (*n* = 63)	*Leigh Hunt B* (*n* = 63)	*Barnes A* (*n* = 60)	*Barnes B* (*n* = 61)	*Maine A* (*n* = 60)	*Maine B* (*n* = 61)
Throat swabs						
No. positive	3	0	2	0	0	0
No. negative	1	6	1	0	4	1
New entrants 1976						
No. of boys with paired sera	22	22	17	21	21	21
% of boys in house	35	35	28	34	35	34
Of those with paired sera 1976						
with antibodies						
No.	3	2	6	6	2	5
%	14	9	35	29	10	24
without antibodies						
No.	19	20	11	15	19	16
%	86	91	65	71	90	76
1977 converted						
No.	7*	4	3	4	0	0
%	32	18	18	19	0	0
% negative who converted	37	20	27	27	0	0

*Includes two boys with positive throat swabs.

suspected enterovirus infections—for example aseptic meningitis—in open wards in hospital.

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Glycosylated haemoglobin levels in children with diabetes mellitus

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SUMMARY Total glycosylated haemoglobin (HbA_1) levels were measured in 94 diabetic children aged between 3 and 19 years. The results were compared with traditional methods of assessing blood glucose control. HbA_1 levels correlated with home urine glucose testing ($P<0 \cdot 05$), with 24-hour urine glucose excretion ($P<0 \cdot 01$), and with height velocity ($P<0 \cdot 001$). Within the first two of these parameters there was a wide scatter of results, suggesting the inaccuracy of these methods for assessing control. The association of raised HbA_1 levels with height velocities < 10th centile shows the effect of poor control on growth. HbA_1 may prove to be an objective method for assessing long-term blood glucose levels in diabetes, and thus it may be possible to determine the effect of good control in the prevention of the various diabetic complications.

The long-term complications of diabetes may have a multifactorial basis and it is still uncertain whether their development is related to blood glucose control. One of the reasons for the difficulty lies in our inability to assess accurately the degree of hyperglycaemia in individual patients. Recently it has been shown that an objective method of estimating control is the measurement of glycosylated haemoglobin (HbA_1) as this compound reflects the mean blood glucose concentration during the previous 2 or 3 months (Koenig *et al.*, 1976b; Gabbay *et al.*, 1977). We therefore examined the correlation between HbA_1 levels and those methods of assessment which are generally used in children with diabetes.

Patients and methods

All the children were attending the paediatric outpatient clinic regularly every 3 or 4 months. Their ages ranged between 3 and 19 years. They were being treated with Monocomponent insulins (Novo Laboratories), once-daily Monotard insulin in the younger children and twice-daily Actrapid and Semitard insulin in the older ones. Control value for HbA_1 levels were obtained in 14 nondiabetic children aged between 5 and 15 years. The controls were randomly selected from children attending the outpatient department; none had any specific disease.

Four methods of assessment were used: HbA_1 levels, twice-daily home urine testing, 24-hour urine glucose output, and height velocity. The home urine tests were those recorded during the previous 3 months before the level of HbA_1 had been examined. The urine tested was the 2nd specimen passed before breakfast and before the evening meal. The results were classified as good (50% or more tests with no glycosuria and <1 in 5 showing 2% glycosuria), fair (<50% tests negative and <1 in 5 showing 2% glycosuria), and poor (<25% tests negative or >1 in 5 tests showing 2% glycosuria). The 24-hour urine glucose output was measured in 82 children and expressed as a percentage of the planned carbohydrate intake. In the prepubertal children the height velocity during the previous year was expressed as a height velocity centile according to age.

Total glycosylated haemoglobins A_{1a}, A_{1b}, and A_{1c} (HbA_1) were measured in duplicate by column chromatography using the method of Welch and Boucher (1978). The results are expressed as a percentage contribution of HbA_1 to the total Hb concentration. The index of precision based on analysis of paired results was ± 0·63% (Whitby *et al.*, 1967).

Results

HbA_1 levels in the control group of children were between 7 and 10% (mean 8·9%). The levels in the

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diabetic children ranged from 8 to 23% (mean 14·7%).

There was a significant difference between the mean HbA_1 levels of those assessed as having good control with home urine tests (mean 13·2%) and those assessed as being poorly controlled (mean 16·4%) ($P<0·05$). There is however a wide scatter in all columns (Fig. 1). Nine of the 13 children assessed as well controlled but with HbA_1 levels above the mean were on once-daily insulin (Monotard), and in 7 of these 9 children the 24-hour urine glucose loss was between 20 and 70% of the planned carbohydrate intake (mean 44%).

A correlation ($r = 0·46$, $P<0·01$) was found between HbA_1 levels and the 24-hour urine glucose output expressed as a percentage of the planned daily carbohydrate intake (Fig. 2).

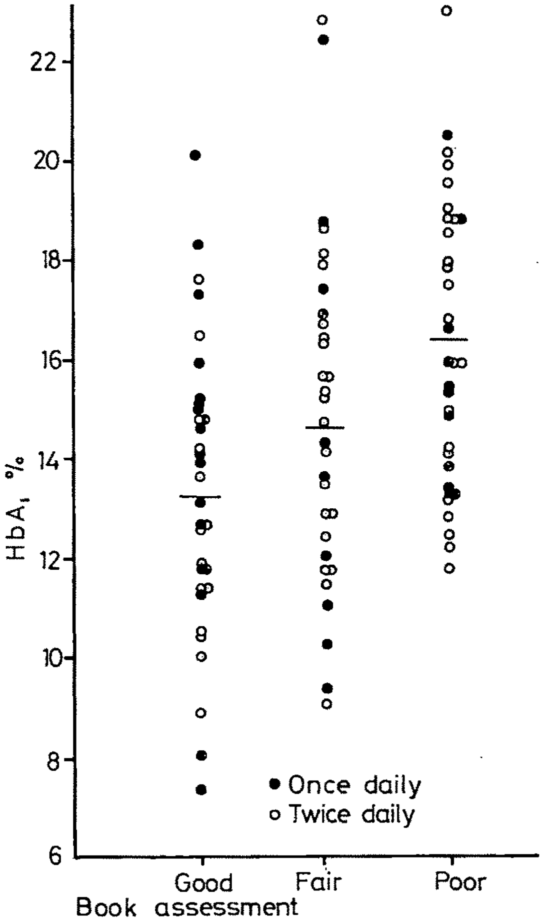

Fig. 1 *Levels of HbA_1 compared with assessment of control by twice-daily home urine tests.*

In those children with height velocity <10th centile, the mean HbA_1 level was 16·2% compared with 12·4% in those with height velocities >10th centile ($P<0·001$) (Fig. 3).

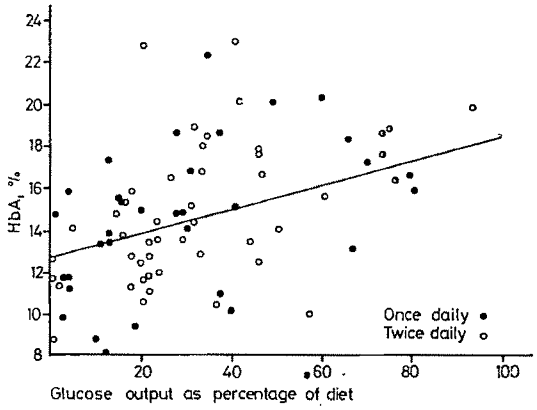

Fig. 2 *Correlation of HbA_1 with 24-hour urine glucose output expressed as percentage of planned carbohydrate intake.*

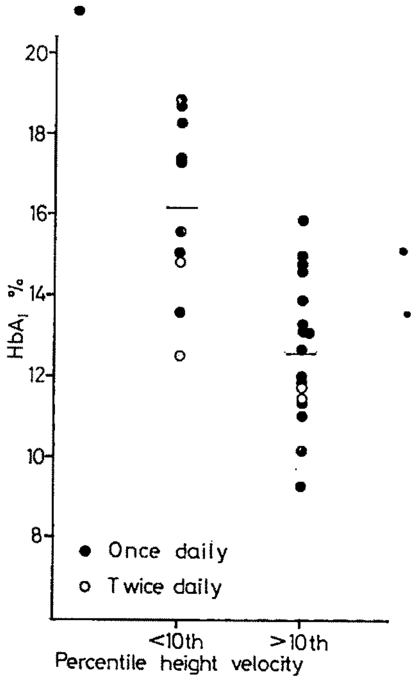

Fig. 3 *Levels of HbA_1 in prepubertal children whose height velocity was less than or greater than the 10th centile.*

Discussion

The glycosylated haemoglobins (A_{1a}, A_{1b}, A_{1c}) are structurally indentical with HbA except for the presence of a glucose group linked to the terminal amino-acid of the β-chain. Glycosylation of HbA occurs by a slow nonenzymatic process in the circulating erythrocyte and forms a stable and relatively irreversible ketamine linkage (Bunn *et al.*, 1976). This results in the continuous formation and accumulation of glycosylated haemoglobins within the erythrocyte during the 120-day life span, and therefore reflects the degree of hyperglycaemia during this period. In health the glycosylated haemoglobins make up less than 10% of the total HbA. Of the 3 glycosylated haemoglobins, HbA$_{1c}$ makes up the greatest fraction and appears to correspond most closely to the degree of hyperglycaemia (Koenig *et al.*, 1976b).

Several investigators have examined the relationship of HbA$_1$ with the more commonly used methods for assessing control in diabetes. They found a correlation of HbA$_1$ levels with physician's rating, urine testing, 24-hour urine glucose estimations, fasting plasma glucose levels, serum triglyceride levels, and response to treatment after diagnosis (Koenig *et al.*, 1976a; Gabbay *et al.*, 1977; Gonen *et al.*, 1977; Lanoe *et al.*, 1977; Peterson *et al.*, 1977; Koenig *et al.*, 1976b; Ditzel and Kjaergaard, 1978). However in nearly all these studies the scatter of results was wide, showing that present methods are inadequate for assessing control in diabetes. Indeed in some studies there was no correlation between the HbA$_1$ level and certain of the parameters used in assessment (Gonen *et al.*, 1977; Lanoe *et al.*, 1977). Overall, however, the evidence suggests that the measurement of HbA$_1$ may be the best method yet available for measuring blood glucose control (Koenig *et al.*, 1976a).

Although we found a correlation of HbA$_1$ levels with our present methods of assessing diabetic control, there is within each parameter a wide scatter of HbA$_1$ levels. This is not surprising as home urine tests are not an accurate method of assessment (Malone *et al.*, 1976), and the measurement of an occasional 24-hour urine glucose output cannot be regarded as an index of day-to-day diabetic control. In a review of studies evaluating the relationship of diabetic control with complications, Knowles (1964) concluded 'the most doubtful measurement of all is that of control'.

An objective parameter in assessing long-term control in children is height velocity. This study shows a clear difference in HbA$_1$ levels between those children who have grown poorly and those with satisfactory growth. Others have not found any correlation between height velocity and traditional methods of assessing control (Jivani and Rayner, 1973; Craig, 1977) which may reflect the inadequacy of these methods, and suggests that HbA is a more accurate method of assessment.

Like others we found that a number of patients thought to be well controlled had raised HbA$_1$ levels. This was particularly apparent in a group of children who appeared well controlled as assessed by home urine tests. In some of these children inaccurate urine testing and book-keeping may account for the discrepancy. However, the majority were young children (<8 years) whose urine tests were generally both checked and recorded by the parents. These children were all on once-daily long-acting insulin injections. This type of insulin controls blood glucose levels between meals but does not prevent the postprandial blood glucose surge (Gokal *et al.*, 1977). Hence, urine tests before meals show little or no glycosuria but miss the marked hyperglycaemia which occurs after each meal. This was reflected in the children's high 24-hour urine glucose output and raised HbA$_1$ levels. It is now our policy to combine a quick-acting soluble insulin (Actrapid) with the once daily long-acting insulin (Monotard) to reduce the postbreakfast hyperglycaemia.

Our data confirm that the measurement of glycosylated haemoglobin may have an important role in evaluating diabetic control. They indicate the limitations of present methods of assessment and show how improbable it is that with these conventional methods we can hope to show a correlation between diabetic control and complications. Prospective longitudinal studies of HbA$_1$ in diabetes may not only provide an objective measurement of overall blood glucose control, but it may also more accurately relate this to the development of the long-term complications of diabetes.

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Drug metabolism in malnourished children: a study with antipyrine

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SUMMARY The effect of malnutrition on hepatic drug-metabolising enzymes was investigated in 8 Sudanese children aged between 9 and 12·5 years using as a model the drug antipyrine. Antipyrine half-life and clearance were measured in the malnourished state and after 3 or 4 weeks of good nutrition. Associated with the improvement in nutritional state was a shortening of antipyrine half-life and an increase in its clearance. There was also a rise in serum triiodothyronine. It is concluded that poor nutrition is associated with impairment of drug metabolic capacity and that many factors are responsible.

Primary malnutrition is the most common medical problem in children in underdeveloped countries (National Institute of Child Health and Human Development, 1971) and is often associated with diseases requiring treatment with drugs. Deficiencies of essential nutrients have been shown to affect the activity of hepatic enzyme systems responsible for drug metabolism. In animal studies dietary withdrawals of protein, vitamin A, thiamine, riboflavin, vitamin C, and minerals have been found to decrease the activity of the mixed function oxidase system of enzymes in the liver and thus to depress the metabolism of certain drugs (Dixon *et al.*, 1960; Kato, 1967; Campbell and Hayes, 1974). Studies in humans deprived of at least one essential nutrient for variable periods have also demonstrated prolonged plasma disappearance of drugs (Conney *et al.*, 1977). In developing countries malnutrition comprises a chronic deficiency of macronutrients and micronutrients, and it is commonly associated with hormone deficiencies (Chopra and Smith, 1975) which in turn can influence hepatic drug metabolism. Alteration in body composition, particularly the presence of nutritional oedema, can also influence plasma disappearance of drugs by changing their volume of distribution.

This study was designed to investigate the effect of established protein-calorie malnutrition on drug metabolism in children and the effect of its treatment. The possible contribution of change in thyroid function to alteration in drug metabolism in malnutrition was also investigated.

Antipyrine was chosen for the study as it is rapidly and completely absorbed after oral administration, is extensively hydroxylated in the liver, is only 10% bound to plasma proteins, and is distributed in body water (Brodie and Axelrod, 1950). Plasma kinetics of antipyrine have been used widely as an indicator of hepatic drug metabolism (Stevenson, 1977).

Patients and methods

Eight children aged between 9 and 12·5 years were studied. In each child protein-calorie malnutrition was established at the beginning of the study. Selection of patients was based on the presence of all the following criteria: history of dietary inadequacy, weight <75% of the standard using the Wellcome Trust classification (*Lancet*, 1970); Hb <10 g/dl, serum albumin <35 g/l (3·5 g/100 ml) in the absence of other causes of anaemia or hypoproteinaemia; presence of signs suggesting vitamin deficiency—for example, angular stomatitis or dry flaky skin. No patient had peripheral oedema or ascites. In 6 patients investigations showed no concurrent disease and there was no recent drug administration. One patient had had malaria which had been treated before the start of the study, and one patient was found to have typhoid fever which was treated with chloramphenicol in the latter part of the study.

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Patients were studied on admission to hospital and again after 3 or 4 weeks on a high-protein, high-calorie diet. The diet contained 5 g protein/kg in the form of meat, fish, and eggs, and adequate amounts of carbohydrates, vegetables, and fresh fruits. Vitamin supplement of the B-group was added with iron in the form of ferrous sulphate.

The following measurements were made: Hb, serum albumin, bilirubin, alkaline phosphatase, aspartate aminotransferase, serum thyroxine (T4), free thyroxine index (FTI), and triiodothyronine (T3). Plasma antipyrine kinetics were performed before and after treatment using the following procedure: after an overnight fast and withdrawal of blood for blank plasma, 600 mg antipyrine as a freshly prepared solution was given orally. Venous samples were drawn at 3, 6, 9, and 24 hours after the dose. Plasma was separated and stored at −20°C for future analysis. Plasma was sent frozen to Bristol for the assay of antipyrine levels using the method of Brodie *et al.* (1949).

Antipyrine plasma half-life ($t\frac{1}{2}$) was calculated from linear regression analysis of the log plasma concentration-time profile. Volume of distribution (Vd) of antipyrine was calculated as dose/plasma concentration antipyrine, extrapolated back to the time of administration. Clearance of antipyrine was calculated as $Vd \times 693 \div t\frac{1}{2}$.

Statistical analysis was carried out using Student's paired *t* test.

Results

The clinical condition of each patient improved during the study period. There were significant increases in weight, Hb, and serum albumin, although mean Hb and mean serum albumin did not reach normal levels (Table 1).

The mean baseline plasma T4 and FTI were normal and the change in these parameters after treatment was not significant (Table 1). However, T3 levels were low at the beginning of the study and rose to normal after treatment.

There were no abnormalities or changes in the levels of alkaline phosphate, bilirubin, or aspartate aminotransferase.

Antipyrine plasma kinetics are shown in Table 2. The mean volume of distribution of antipyrine was higher after treatment, but the difference was not significant and disappeared when corrected for change in body weight. There was a significant 33% shortening of antipyrine plasma half-life, and a significant 64% increase in plasma clearance after treatment for malnutrition.

Discussion

This study showed that drug metabolism is impaired in malnourished children and that impairment can be reversed within a month of starting an improved diet. Such a finding has not been previously reported.

The main observation is the shortening of antipyrine half-life and the increase in its clearance which occurred between measurements in the malnourished and treated states. In most patients the only treatment was dietary replacement. Two patients were receiving treatment for malaria and typhoid which might have influenced antipyrine kinetics. However, if these patients are excluded the change in antipyrine half-life is still significant. It is reasonable to conclude that the change in antipyrine kinetics

Table 2 *Antipyrine disposition in 8 children with malnutrition before and after treatment*

Case	*Treatment*	*Sex*	*Volume of distribution (l)*	*Half life (hours)*	*Clearance*
1	Before	M	20·8	27	9
	After		27·3	13·5	23·3
2*	Before	M	15·8	16·5	11·1
	After		35·3	12	33
3	Before	F	11·5	15	9
	After		14·3	14	11·8
4	Before	F	21·4	7·8	31·7
	After		15	5·4	32·1
5	Before	M	27	18·6	17
	After		24	13·5	20·7
6**	Before	M	21	9·1	26·7
	After		25·6	6·7	44
7	Before	M	18·8	9	24
	After		20	6·8	44
8	Before	M	36·6	15·4	27·4
	After		38·7	7·6	58
Mean	Before		21·7±2·7	14·8±2·1†	19·5±3·2†
±SEM	After		25 ±3·1	9·9±1·3	32 ±5·1

†P<0·05
*Patient with typhoid, **patient with malaria.

Table 1 *Comparative clinical and biochemical data on 8 children with malnutrition before and after treatment*

	Weight (kg)	*Hb (g/dl)*	*Serum albumin (g/l)*	*T4 (nmol/l)*	*FTI*	*T3 (nmol/l)*
Before treatment (mean ± SEM)	24·7 ± 1·4*	7·3 ± 0·2*	28·3 ± 3·0†	117 ± 7·8	121 ± 6·6	0·69 ± 0·1†
After treatment (mean ± SEM)	29·5 ± 1·8	10 ± 0·4	33·9 ± 3·3	130 ± 11·4	129 ± 10·9	1·96 ± 0·2

*P = 0·001, †P<0·05.
Conversion: SI to traditional units—T4: 1 nmol/l ≈ 0·078 μg/100 ml; T3: 1 nmol/l ≈ 0·65 μg/ml.

during the study period was related to altered nutritional state and that the results obtained at the beginning of the study reflected abnormally depressed drug metabolism due to nutritional deficiency. Evidence of an improvement in nutritional state is provided by the changes in bodyweight, Hb, and serum albumin levels.

The results of this study differ from those of Krishnaswamy and Naidu (1977) who compared groups of normal and malnourished adults. In their study the antipyrine half-life was normal in undernourished patients and was prolonged only in patients with nutritional oedema, possibly due to altered volume of distribution. However, exposure to environmental enzyme-inducing factors could not be excluded. In the present study the within-patient comparison excludes all such environmental factors. Furthermore the absence of change in volume of distribution, and the pronounced increase in plasma clearance of antipyrine with nutritional replacement, support the concept that malnutrition decreases the drug-metabolising capacity of the liver.

It is not possible to say which factor in the malnourished children was most responsible for the decreased drug metabolism, and it is likely that they were deficient of many of the essential nutrients which have been shown to affect hepatic enzyme systems. The reduced serum albumin provides evidence of protein malnutrition which may cause a reduction in total amount of microsomal enzymes. In the rhesus monkey, protein deprivation resulted in loss of liver weight with an associated decrease in concentration and activity of microsomal enzymes (Rumack *et al.*, 1973), and in rats protein deficiency induced fatty infiltration of the liver with reductions in the number of functioning cells and in total microsomal protein content (Campbell, 1977). Protein deficiency has also been shown to decrease *in vitro* microsomal oxidation of strychnine, aminopyrine, and ethyl morphine, and to reduce cytochrome P450 content (Campbell and Hayes, 1974).

The children in the present study received supplements of vitamin B, vitamin C-rich fruits, and oral iron. Drug-metabolising enzyme systems have been shown to be highly dependent on vitamin C status in animals (Campbell and Hayes, 1974). Supplementation of the diet of normal individuals with vitamin C has resulted in a substantial increase in antipyrine clearance (Houston, 1977), and vitamin C deficiency is partly responsible for the retardation of drug clearance in elderly people (Smithard and Langman, 1977), and in patients with liver disease (Beattie and Sherlock, 1976). It is possible that the vitamin supplements in this study accounted for some of the observed improvement in antipyrine clearance. As there is evidence that iron deficiency enhances drug metabolism (Langman and Smithard, 1977), the iron supplements are unlikely to have contributed to the change.

The findings of low T3 levels in the face of normal T4 and FTI in the malnourished children is in agreement with the results of other workers (Pimstone *et al.*, 1973; Chopra and Smith, 1975). It has been suggested that the low serum T3 level is due to a reversible defect in the extra-thyroidal conversion of T4 to T3 (Chopra and Smith, 1975). Similar results have been observed in patients with anorexia nervosa when the biotransformation of labelled testosterone and oestradiol was impaired in all patients studied. Drug metabolism was restored to normality by the administration of T3 and by reversion of thyroid function tests to normal after good nutrition (Fishman *et al.*, 1977). It is possible therefore that the low T3 levels in the present study could be a factor in the prolongation of antipyrine half-life.

The present study has shown a reduction in the metabolism of antipyrine in malnourished children which is reversible by proper nutrition. Many factors may have contributed to this finding. Dose requirements of drugs metabolised by microsomal hydroxylation in the liver in children are dependent on nutritional status.

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The following articles will appear in future issues of this journal:

Osteoid osteoma and benign osteoblastoma in childhood. *J. A. Black, R. K. Levick, and W. J. W. Sharrard.*

Clinical events relating to intraventricular haemorrhage in the newborn. *M. Fujimura, D. M. Salisbury, R. O. Robinson, P. Howat, P. Emerson, J. W. Keeling, and J. P. M. Tizard.*

Lipoprotein measurements—a necessity for precise assessment of risk in children from 'high-risk' families. *D. Heldenberg, I. Tamir, O. Levtow, Y. Burstein, and B. Werbin.*

Giant exomphalos—conservative or operative treatment? *D. C. S. Gough and A. W. Auldist.*

Absorption of chlorhexidine from the intact skin of newborn infants. *Jennifer Cowen, S. H. Ellis, and J. McAinsh.*

Premature menarche without other evidence of precocious puberty. *M. E. Heller, John Dewhurst, and D. B. Grant.*

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Personal practice

Mourning by the family after a stillbirth or neonatal death

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SUMMARY Failure of the parents to mourn after the sorrow of a stillbirth or neonatal death can result in dire consequences for the well-being of the family. Doctors and nurses should learn how to facilitate mourning and should accept the strange and sometimes bizarre forms this may take. When mourning is facilitated, the family is likely to adjust better to its bereavement.

Stillbirth is a common tragedy occurring in about one in 100 deliveries. Yet after a stillbirth everyone tends to behave as if it had not happened. In hospital bereaved women are usually isolated and avoided and then discharged as soon as possible. Although this is meant kindly, to protect the mothers from the painful awareness of live babies, it also means that the hospital staff do not have to face their own anxiety about stillbirth. Back at home, the family, friends, and professionals continue to avoid talking to the bereaved mother, depriving her of the talk that would help her mourn. There is silence. Statistical evidence shows that family doctors are astonishingly reluctant to know or remember anything about the patient who has a stillbirth (Bourne, 1968). This avoidance by the helping professionals extends into neglect of the study of the effect of stillbirth on the mother and the family. There is a conspiracy of silence. We seem unwilling to come to terms with the fact that it is a tragedy which can seriously affect the mental health of a bereaved mother and her family. After the failure to mourn a stillbirth, mothers can have psychotic breakdowns or there can be severe marital difficulties. Children born before or after a stillbirth where there has been a failure to mourn the stillbirth, can have severe emotional difficulties. Many mothers have mothering difficulties with the child born subsequently (Lewis and Page, 1978). The surviving twin of a stillbirth faces profound difficulties in life.

The psychoanalytical view of mourning is of an ongoing process during which the conscious and unconscious mind works on coming to an understanding of the memories, thoughts, and feelings about the dead person. The dead person is unconsciously imagined as being taken inside our mind and our body. The dead can be felt as dead inside us. We identify with the dead person. Doctors meet this phenomenon when a bereaved person develops imaginary symptoms related to the illness of the dead person. During the work of mourning we digest our memories and feelings about the dead and free ourselves from the identification. With incomplete or failed mourning the identification can persist and result, for instance, in a depressive illness with somatic symptoms. Or a failure to come to terms with our inevitably mixed feelings for the dead can lead to a denial of negative feelings and an overemphasis of positive feelings. A potentially dangerous idealisation of the dead person can result. When a mother idealises her dead child there can be dire consequences for the mothering of her subsequent children.

It is the nature of stillbirth that leads us all to avoid the subject. Bourne (1968) described stillbirth as a nonevent in which there is guilt and shame with no tangible person to mourn. A stillborn is someone who did not exist, a nonperson, often with no name. It is an empty tragedy and a painful emptiness is difficult to talk about. After a stillbirth there is a double sense of loss for the bereaved mother who now has a void where there was so evidently a fullness. Even with a live birth the mother feels a sense of loss but the consolation of a surviving 'outside baby' helps the mother to overcome her puzzling and

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bewildering sadness at losing her 'inside baby' (Lewis, 1976a). With a stillbirth, the mother has to cope with an outer as well as an inner void. There is an even more puzzling sense of nothingness for a mother who is anaesthetised at delivery—for example with a caesarean section.

Memory facilitates the normal mourning processes essential for recovery. With other bereavements there is much to remember. These memories can be shared and cried over with family and friends. Not so with stillbirth—there is no one to talk about and no one to talk to about it. The bereaved mother may herself avoid contact with people because of unconscious feelings of shame and guilt. Her shame is associated with the sense of having failed as a woman. She may feel that there is something wrong with her womb. Her guilt has to do with fantasies that her thoughts or actions have caused the death—for example, by having considered a termination of pregnancy or by having sexual intercourse late in pregnancy. If we allow mothers to isolate themselves we may seem to be confirming that their shame and guilt are justified. Many bereaved mothers keep their distress to themselves, not only to avoid too intense an awareness of their loss, but to protect others from distress. By so protecting others they deprive themselves of the talk which would aid mourning. And of course husbands and children also have their guilt about a stillbirth because of their mixed feelings about the pregnancy. This impedes their mourning.

To facilitate mourning I recommend that a stillbirth be managed by making the most of what is available and can be remembered. The aim is to fill the emptiness that impedes mourning (Lewis, 1976b). Bereaved parents should be encouraged to help lay out their dead baby. A post-mortem photograph, examination, and *x*-ray will assist genetic counselling. Parents should also be persuaded to take an active part in the certification of stillbirth, to name the baby, and to make the funeral memorable. The practice of burial in a common and nameless grave should be avoided. The family should be encouraged to attend the funeral or cremation and to know of a marked place or grave. Other children in the family find the idea of a stillbirth incomprehensible and frightening. Yet it is they, in particular, who tend to be left in the dark about the stillbirth, left without help with their grief.

It is my impression that if a stillbirth has been a real experience for the family in the ways that I have described, mourning will have been facilitated. This leads to fewer psychological problems for the mother and her family. When a stillbirth is managed in the way that I have suggested I believe that it is a helpful experience for staff and patients. However there is a need to be prepared for some upsetting and crazy experiences. The management of stillbirth causes considerable anxiety, particularly if the child is macerated as a result of intrauterine death or is malformed (Lewis, 1978). For this reason it is helpful if those managing such a painful happening as a stillbirth can have discussions with staff who have had experience of it. The reaction of parents and staff themselves to stillbirth and neonatal death can be disconcerting. The normal reactions to bereavement *are* disconcerting. Freud (1957) said of normal mourning that it would seem like an illness were we not aware of the bereavement. Most people know little of the natural history of the normal reactions of parents handling their dead babies.

With stillbirth or neonatal death, it is partly the loss of what might have been, the loss of experience in the future, which makes them such heart-rending and deeply frustrating experiences.

A baby of 27 weeks' gestation was resuscitated several times in the 10 days it survived. The mother had seen the baby collapse and thought it dead, but it was resuscitated to live a short time. With difficulty, the ward sister was able to arrange a funeral and cremation for this baby, even though it was under 28 weeks' gestation. The baby was laid out in the incubator. The mother was encouraged first to touch and then to hold him. She became frenzied, clutching her baby, and then stripping the clothes off. She kissed his navel and his penis. She forcibly opened his mouth and said, 'That's where his teeth would have been'. Then she 'walked' her baby on the floor. Soon the mother calmed down and gave the baby back to the sister. The sister was distressed but when later the parents came to see her, her impression was that this mother was coping better than many bereaved mothers.

The detailed study of the natural history of bereavement has shown that many seemingly crazy ideas and actions are within the normal range of responses to loss (Parkes, 1972). Although this mother's behaviour appears mad, if we examine it more closely we can see the sense in her behaviour. She was attempting to come to terms with the baby's lost future. In her mind she maintained the continuity of the cycle of life. By kissing the umbilicus she was remembering her creative link with the baby *in utero*; kissing the mouth may be linked to the kiss of life, to the resuscitation. The mother longed for her son to grow teeth and learn to walk, and kissing his penis could be considered a wish to restore her dead son's potential capacity to create life. Creating memories about her baby in this way facilitated mourning.

A nurse, a senior sister, suggested that the parents of a dying, severely brain-damaged 'prem' look at and touch their baby. Knowing that the mother had wanted to breast feed her baby, the nurse suggested that the mother might take off her blouse and hold her baby close to her skin. This suggestion by the nurse seems to ignore the critical state of the infant, and may have been provoked by her wish that this virtually dead baby might live. To the nurse's consternation the mother put the dying 'prem' to her breast, expressed milk into the infant's mouth, and then moved its mouth to encourage swallowing. When the baby died the parents washed and dressed him in the baby clothes that the nurse had suggested they bring with them. In her next pregnancy this mother's memory of her dead baby was of cradling him in her arms. So far, although at times tearful when remembering her dead child, she is making a good job of the mothering of her new baby. While the nurse went further than I would have advised out of my concern for the physical management of the admittedly moribund baby, nevertheless she may have helped the mother when the baby was beyond medical help.

A 28-week premature baby died at 3 days. The mother telephoned the nurse who suggested that the parents come to see their dead baby son. The mother asked if she could bring baby clothes and the nurse agreed. The nurse took the parents to the viewing room by the mortuary. They dressed their baby and told the nurse the baby's name. After this sort of experience with their dead baby many parents, because they find it helpful, keep in touch with the staff. The mother later visited the unit and asked the nurse whether she considered blue a morbid colour to paint their living room. She also said that she was learning to crochet. It seems to me that this mother was thinking about the blues, and perhaps associating blue with boys, and her dead son. She may also have been asking permission to go on living, to improve her living room, which unconsciously was probably symbolic of her womb, just as learning to crochet may have been symbolic of her making a new baby. She seemed to be asking the nurse if she could be considered the sort of woman who could be trusted with another baby. Unconscious destructive feelings to a lesser or greater extent are always present as part of the normal mixed feelings that a mother has about her pregnancies. After the baby died this mother feared that her unconscious destructive feelings were a reason for the child's death. Because of this she seemed to need the nurse's reassurance about her baby-making ability versus her destructiveness.

I am loath for parents to rush into pregnancy after a stillbirth until they feel that they have adequately mourned their dead baby. They need time to think through and come to terms with the stillbirth, and to understand how to avoid the idealisation of a dead baby that so often bedevils the life of subsequent children.

A premature baby died. The father gave away the baby clothes etc. The mother went home, took out a small bundle of baby clothes that she had hidden away, guessing that her husband might give the baby things away, and cried over the clothes.

The wife of a medical student studying anatomy had a stillbirth. He remarked to a fellow student that he wanted to get hold of his stillbirth to dissect it. His colleague was amazed, but now understands the father's need to have some tangible experience of his stillborn child, so as to facilitate mourning. This story seems upsetting but is an example of how bereaved parents will seek of themselves to get an experience of their stillborn, sensing that this will help them to mourn. Obviously this father would have benefited from other help.

Similarly many mothers seem to know that it would be helpful to look at their dead baby, although they are usually put off when they ask hospital staff whether they should do so. One mother in trying to get an experience of her stillborn child made the most of what she had seen—a cot and a wisp of black hair on the top of his head. This is now a dear memory for her.

A photograph of a dead baby can help parents who have been unable to see their stillborn child. Or other eyes that have seen can tell the parents. A husband carefully described to his wife how his stillborn daughter had looked, described her face and hair, her delicate normal body and limbs, and also the dark-stained blotches on one side.

A woman house surgeon did something like this for the parents of an anencephalic baby which her consultant had refused to allow her to show the parents. She described to the mother and father the normal body, the normal delicate hands and fingers, legs, feet, and toes of the anencephalic baby. The doctor also encouraged the father who had wanted to protect his wife by leaving her out of the funeral, to take her along. The doctor said it was also the mother's baby and so the father did take his wife to the funeral.

It is necessary to make recommendations about the management of stillbirth in hospital. I believe that parents left to themselves, and this is particularly so with domiciliary delivery, would do things better. You may feel that my suggestions about the management of stillbirth and neonatal death are silly. But I suggest that the normal 'rugby pass' management of stillbirth in hospital is rather more bizarre. I refer to the catching of a stillbirth after delivery, the quick accurate back-pass through the labour room door to someone who catches the baby and rapidly covers it and hides it from the parents and everyone. Our hospital culture tends to impede the normal healing process of mourning. We do this even by asking the mother whether she wishes to see her dead baby. Really what could be more natural? It heartens me when I hear of a father describing the baby in detail to his wife, of the mother who hid the baby clothes to cry over, or of the father who wished to dissect his baby, or of the mother who kissed and walked her dead baby. Sometimes people know how to help themselves. It is difficult in hospital. A senior midwife was encouraged by the obstetrician to show a stillbirth to the parents. She took the macerated stillbirth out of the labour room saying, with the irony of the unconscious, that 'to show them the baby would put them off stillbirth for life'. Fortunately this midwife recovered, brought the baby back to the parents and, with great sensitivity, showed them the normal limbs, fingers, and toes, and asked them the name of the baby.

In the Far East there is a cactus with white fragrant flowers that blooms briefly only every few years. Each bud opens and dies visibly in front of one's eyes within a few hours. A family may sit together and watch the birth and death of the flower, for it brings good luck. A Far Eastern couple buried their stillborn in a little grave with a small headstone inscribed with the name of this cactus given to their child. An act of creative poetic self-healing.

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Short reports

Improved accuracy of continuous measurement of arterial oxygen tension in sick newborn infants

Criteria for reading and recalibrating the electrode

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SUMMARY Improved accuracy of continuous arterial oxygen tension (Pao_2) measurement is obtained if allowance is made for the response time of the electrode. Recalibration is necessary only when Pao_2 measured in a blood sample differs from the electrode value by more than ±11·5 mmHg (1·5 kPa).

During the last 6 years continuously-recording intravascular oxygen electrodes have been developed (Parker *et al.*, 1971; Harris and Nugent, 1973; Goddard *et al.*, 1974). These instruments have shown that the arterial oxygen tension (Pao_2) in sick newborn babies may fluctuate widely, and that analysis of intermittent blood samples is often a poor reflection of the changes taking place. The ideal continuously-recording oxygen electrode would be accurate and reliable, and would not introduce any hazards that do not already exist with an umbilical arterial catheter (Kollmeyer and Tsang, 1974). Accuracy depends on the initial calibration against blood analysis of Pao_2, while reliability depends on knowing when to recalibrate.

Of the various electrodes that have been developed only one is commercially available.* We have devised a technique that greatly improves the accuracy of this instrument and we also report our criteria for recalibrating the electrode.

The instrument

The electrode is attached to the end of a 5 French gauge (1·67 mm) dual-lumen polyvinylchloride catheter. One lumen has a side hole and is used for blood sampling, fluid infusion, and pressure measurement. The other lumen contains the leads from the polarographic oxygen electrode which are connected to a battery-powered amplifier. A meter displays the reading of Pao_2. An optically-coupled recording unit enables a continous chart record of Pao_2 to be made. The output current of each electrode is tested before the catheter is individually packed and sterilised.

After the catheter has been inserted there is a gradual change in sensitivity of the electrode caused by membrane thickening as water is absorbed, and it is recommended that the electrode be calibrated after 15–30 min. The meter is read and a sample of blood is withdrawn for Pao_2 measurement. When the result is known the meter reading is adjusted by the ratio of the blood Pao_2 to the meter Pao_2. The accuracy of this method of calibration depends on the response time of the system and on any change in Pao_2 just before, or during, blood sampling. The electrodes used in this study had a 95% response time of between 40 and 60 seconds.

Patients

We placed 28 catheters in 24 newborn infants (birthweights between 0·6 and 3·6 kg, mean 2·15); each required an indwelling arterial catheter for clinical management. Most infants were born prematurely, with a mean gestational age of 34 weeks (range 24–44). 15 had birth asphyxia, 5 developed severe hyaline membrane disease, and 5 severe haemolytic disease; 4 had meconium aspiration, 2 polycythaemia, and one each, diaphragmatic hernia, delayed resorption of lung fluid, and viral pneumonia. Three infants died in the neonatal period.

We obtained consent from the parents to use this type of catheter instead of the standard polyvinylchloride umbilical arterial catheter†; often this was obtained some days before birth if there was premature labour or if elective caesarean section was planned.

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*G. D. Searle & Co. Ltd., High Wycombe, Bucks.

Methods

We have already described our technique for catheterisation of umbilical arteries (Kitterman *et al.*, 1970). No alteration in our routine procedure was made and during this initial evaluation we did not rely on the continuous reading of Pao_2 for clinical management, but continued to sample blood at least every 4 hours for measurements of Pao_2, $Paco_2$, and pH (Radiometer PHM72).

The electrode was calibrated as soon after insertion as possible and a continuous record of Pao_2 made on a polygraph recorder (Grass model 7A). From this record it was apparent that Pao_2 was fluctuating, often by as much as 20 mmHg (2·7 kPa), even when the baby was sleeping and breathing quietly. In these circumstances if blood is sampled for analysis of Pao_2, the meter will read the correct value only after the response time of the electrode has elapsed. The meter reading at the time blood is being sampled will not reflect actual Pao_2 and this discrepancy may lead to unnecessary recalibration. During this study we read the meter at the time blood was sampled and then we allowed for the response time of the electrode and read it again 45 seconds after blood sampling. The Radiometer electrode value for Pao_2 was compared with the meter readings and the differences calculated. When the difference, even after allowing for the response time, was greater than 10 mmHg (1·34 kPa) we repeated the blood sample. In most cases the discrepancy between the meter reading and the Pao_2 in this second sample was <10 mmHg but if it again exceeded 10 mmHg we recalibrated the electrode. This decision was based on our feeling that when a discrepancy of >10 mmHg exists between the predicted value (catheter electrode) and actual value (Radiometer) of Pao_2, then the usefulness of the electrode for regulating oxygen and artificial ventilation, and for safely reducing the frequency of blood sampling is seriously diminished.

Results

Four of the 28 electrodes did not activate. The mean time to initial calibration of the remaining 24 electrodes was 74 minutes (range 18–240). Delay was in most cases due to a very unstable Pao_2 immediately after birth and during resuscitation.

The catheters were in place for between 2 and 135 hours (mean 43). During this time haematocrit varied between 18 and 72%, $Paco_2$ between 15 and 88 mmHg (2–11·7 kPa), and pH between 7·06 and 7·57. The Pao_2 meter was read at the time of blood sampling and 45 seconds later on 408 occasions. Eight electrodes were recalibrated, 7 once, one twice. Mean time between calibrations was 38 hours.

Fig. 1 shows the correlation between the Pao_2 values from the blood sample and the meter reading of the Pao_2 electrode (a), at the time of sampling and (b) 45 seconds later.

The relation between Pao_2 recorded by the Radiometer electrode and the catheter electrode is described by the equations:

(a) Simultaneous reading
$y=8{\cdot}35+0{\cdot}86x$ ($r=0{\cdot}867$. SE of regression $=9{\cdot}15$)

(b) Reading at 45 seconds
$y=2{\cdot}29+0{\cdot}97x$ ($r=0{\cdot}948$. SE of regression $=5{\cdot}84$).

The value of Pao_2 read at 45 seconds is a significantly better estimate of the true Pao_2 value ($F=2{\cdot}45$, $P<0{\cdot}001$). When this reading of Pao_2 at 45 seconds (Fig. 1 (b)) is used to predict the true Pao_2 value, the meter reading has 95% confidence limits for regression of ± 11·5 mmHg (1·5 kPa). This compares with a value of ± 17·9 mmHg (2·4 kPa) for the reading in the time of sampling (Fig. 1 (a)).

The differences between individual values for Pao_2 read by the electrode at 45 seconds and the Radiometer Pao_2 value ranged from 0 to ± 21 mmHg (2·8 kPa) within the preset limits of two consecutive values >10 mmHg (our criteria for recalibration). The SD of the differences was ± 5·6 mmHg (0·75 kPa). Fig. 2 shows an example of one electrode's performance plotted to show the variation in the prediction of actual Pao_2 and an example of recalibration. The 95% confidence limits for regression of ± 11·5 mmHg (1·5 kPa) defines the limits that may be used without the need to repeat a blood sample.

Discussion

Continuous recording of Pao_2 in sick newborn infants is potentially a method by which oxygen tension may be kept within safe limits while, at the same time, reducing the number of blood samples taken and hence the need for transfusion of blood.

To achieve this, the electrode when accurately calibrated must remain stable, and the frequency of recalibration be reduced to a minimum. An unduly long response time can lead to incorrect calibration,

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†Argyle Umbilical arterial catheter ALOE Medical Co. St Louis.

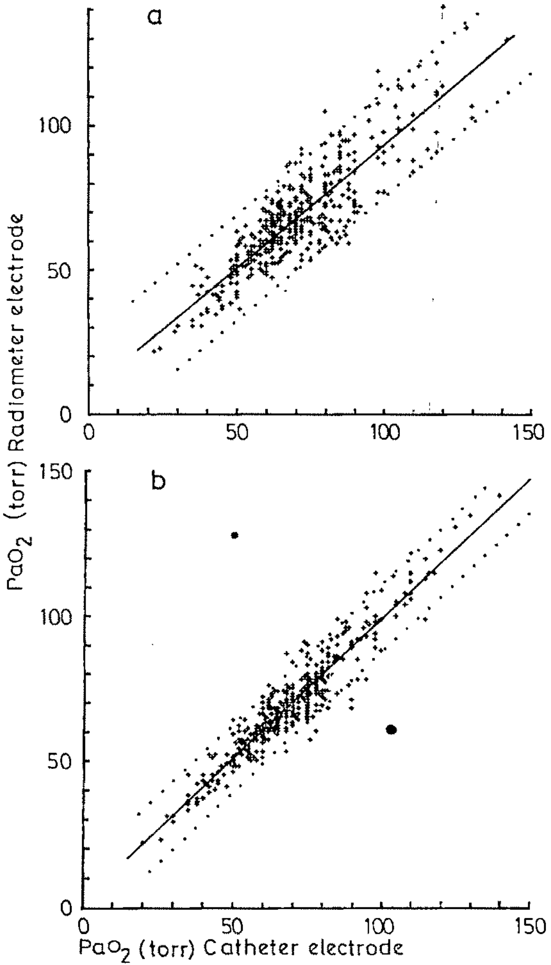

Fig. 1 *Relation between PaO_2 reading from catheter electrode and PaO_2 in a blood sample measured by Radiometer electrode. (a) Electrode reading at time of blood sampling. (b) Electrode reading 45 seconds after blood sampling. 95% confidence limits are shown.*
Conversion: 7·5 torr (7·5 mmHg) = 1kPa.

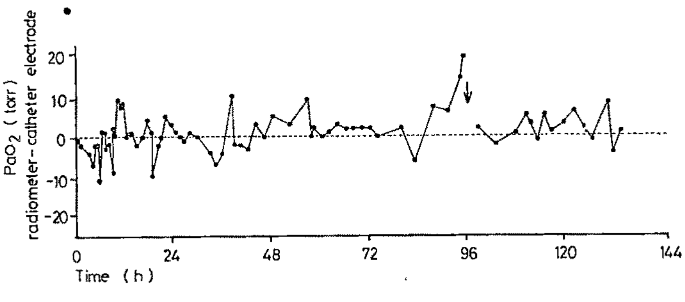

Fig. 2 *Example of sequential difference between PaO_2 reading from catheter electrode and PaO_2 in blood sample measured by Radiometer electrode. Electrode recalibrated at arrow.*

especially if PaO_2 is changing during sampling. In a preliminary study of this problem, Rolfe (1976) using a similar electrode, reported differences of −13 to + 19% despite recalibrating the electrode after each of 6 blood samples during a 3-hour period.

We have shown that greater accuracy and therefore a reduced frequency of recalibration may be obtained by allowing for the response time of the system by reading the meter 45 seconds after blood sampling.

When used in this way recalibration is only required when the meter reading differs from Pao_2 in a blood sample by more than ± 11·5 mmHg (95% confidence).

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Haemorrhage responsive to vitamin K in a 6-week-old infant

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SUMMARY A 6-week-old breast-fed infant presented with vomiting, jaundice, and irritability. Haemorrhage occurred after lumbar puncture, and a coagulation abnormality which responded to vitamin K was found. It would seem prudent to estimate the prothrombin time before invasive procedures in breast-fed infants of this age, or to give vitamin K to such infants when doubt exists about previous vitamin K administration.

Case report

A term baby boy weighing 3450 g was delivered after spontaneous onset of labour to a primagravid mother. Apgar scores were 3 at one minute and 5 at five minutes. He was resuscitated with oxygen delivered by face mask. Mild, presumed physiological jaundice developed on day 3 but otherwise the neonatal period was uneventful. Neither mother nor baby received vitamin K. He was breast fed. Slight jaundice persisted after his discharge on day 5 but he remained well until admission at 6 weeks with a 2-day history of nonprojectile vomiting after feeds without haemorrhage. For 5 days there had been slight irritability on handling, but sleep, feeding, and bowel function were all normal. The icterus had intensified. There was no history of maternal or infant drug ingestion, but both parents had developed upper respiratory tract infections 5 days previously.

On admission the baby was afebrile, slightly jaundiced, mildly dehydrated, and irritable on handling. Weight was on the 50th centile with length and head circumference on the 90th centile for age. The anterior fontanelle was full but not tense. Systematic and neurological examination, including fundoscopy, were normal. No clinical evidence of pyloric stenosis was detected. Initial investigations included a haemoglobin of 9·1 g/dl, a white blood count (WBC) of $9 \cdot 2 \times 10^9/l$ ($9200/mm^3$) (neutrophils 35%, lymphocytes 65%), and a platelet count of $360 \times 10^9/l$ ($360\,000/mm^3$). The film contained a few atypical lymphocytes. Serum electrolytes were within normal limits. Serum total bilirubin was 90 μmol/l; 5·3 mg/100ml (direct 39 μmol/l; 2·3 mg/100ml). Full infection screen, including CSF analysis, showed no evidence of a bacterial infection.

Within 8 hours he became pale and lethargic. An extensive haematoma at the lumbar puncture site and oozing from the venepuncture site were noted, but no petechiae or ecchymosis. He remained afebrile. His haemoglobin had fallen to 7·4 g/dl, the WBC had risen to 13·9 × 10^9/l; 13 900/mm^3 (neutrophils 53%, lymphocytes 38%), and the platelets were 450 × 10^9/l (450 000/mm^3). His blood film showed no evidence of red cell fragmentation nor of toxic neutrophil changes. Coagulation screen showed a prothrombin time of 300 seconds (control 13 s), a PTTK of 120 seconds (control 37 s) and serum fibrinogen of 1·7 g/l; (170 mg/100ml). His serum electrolytes were unchanged. The direct Coombs's test was negative and the serum bilirubin was unchanged. Hepatic enzymes showed no increase with an ALT of 49 units/l and an AST of 52 units/l (normal values for each 5–120 units/l). Serum alkaline phosphatase was 599 new units/l. Serum T4 was 150 nmol/l (11·65 μg/100ml). Urine contained no reducing substances and there was no evidence of bacterial or viral pathogens from cultures of urine, stools, blood, or throat and nose swabs. There was no alteration in viral titres to CMV, herpes simplex, rubella, and toxoplasma. He was Australia antigen negative. Maternal prothrombin time was 15 seconds. Treatment included transfusion with packed red cells (80 ml), 2 mg IV vitamin K, and gentamicin, cloxacillin, and IV fluids. Within 12 hours the prothrombin time was corrected to 15 seconds (control 15 s), the PTTK to 34 seconds (control 35 s), and the haemoglobin raised to 10·7 g/dl. There was no other alteration in the coagulation screen. Fibrin degradation products were normal throughout. No further bleeding occurred. Mild fever persisted for some 3 days but without emesis. Weight gain continued with breast feeding and he showed no further clinical or laboratory disturbance of coagulation during the ensuing week. One week after admission serum bilirubin had fallen to 19 μmol/l (1·1 mg/100ml).

Two months later he was thriving with no further haemorrhagic sequelae.

Discussion

This infant presented with vomiting and an increasing jaundice at 6 weeks. No evidence of bacterial infection was found and, although no viruses were isolated, there had been a presumed viral infection in the family and, in addition, atypical lymphocytes were seen on the blood film.

The prolonged neonatal jaundice may have been related to breast feeding or liver immaturity but normal liver enzymes excluded gross hepatic disease. There was no evidence of congenital infection galactosaemia, or hypothyroisidm. The jaundice may have been exacerbated by decreased fluid intake, and emesis with the infection.

We presume that the bleeding after lumbar puncture was related to vitamin K deficiency in view of the prolonged prothrombin and partial thromboplastic times and their rapid correction with vitamin K.

Normal platelet counts, serum fibrinogen, fibrin degradation products, and blood film excluded a consumptive coagulopathy. There was no maternal history of any drug ingestion.

In classical haemorrhagic disease of the newborn, bleeding occurs as a result of deficiency of vitamin K-dependent clotting factors and is virtually confined to breast-fed babies. It is preventable if vitamin K is given at birth. A haemorrhagic syndrome with a similar coagulation abnormality occurs beyond the neonatal period, usually between 4 and 12 weeks.

Factors which have been previously implicated are: (1) decreased vitamin K intake due to breast feeding; (2) prolonged diarrhoea; (3) antibiotics causing an alteration in gut flora. Nammacher *et al.* (1970) described 4 such infants aged between 5 and 8 weeks. None had been given vitamin K at birth and 3 were breast fed; 2 had intracranial bleeding and the coagulation abnormality was corrected with vitamin K in all 4. Other cases have been similarly described in association with diarrhoea and antibiotics (Goldman and Deposito, 1966).

In this case, the baby had not received vitamin K at birth and was entirely breast fed with a presumed defective vitamin K intake. Breast milk contains 15 μg/l vitamin K whereas cows' milk has a higher level of 60 μg/l. He had not been given antibiotics nor had he had diarrhoea. It would appear that breast feeding alone was responsible for his vitamin K deficiency state, and perhaps the coagulation abnormality would not have come to light had he not developed an infection necessitating lumbar puncture and venepuncture.

We thank Dr D. G. D. Barr for permission to report this case.

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Cervical lymphadenitis in childhood due to mycobacteria of the Fortuitum group

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SUMMARY Two children with cervical lymphadenitis due to *Mycobacterium fortuitum* infection are described; both presented with erythema nodosum.

Opportunist mycobacteria which grow rapidly at 37 and 25°C and lack pigment, belong to the Fortuitum group (Marks, 1976). Infection is rare in man and it usually follows injections (Beck, 1965) or trauma (Hand and Sanford, 1970). We report 2 children presenting with cervical lymphadenitis and erythema nodosum due to Fortuitum group organisms. This has not been previously reported.

Case reports

Case 1. A 5-year-old girl from mid-Glamorgan presented in November 1977 with bilateral cervical swellings fluctuant on the left, fever, and erythema nodosum. There was no family history of tuberculosis. The Mantoux test with 1 TU PPD was strongly positive but *x*-rays of the chest were normal. The left-sided cervical abscess was incised and drained (Mr J. Lari). The pus showed numerous acid- and alcohol-fast bacilli on microscopical examination and within 7 days an organism belonging to the Fortuitum group was grown. It was resistant to all antibiotics except ethionamide, gentamicin, and amikacin. Initially the patient's condition improved after operation on standard antituberculous treatment (rifampicin, isoniazid, and ethambutol). However, the fever returned and she developed an abscess on the right. This was incised and drained (Mr J. Lari), and the treatment changed to ethionamide 125 mg twice daily, and gentamicin 40 mg three times daily, the latter for 10 days. She became afebrile on this regimen and the swelling subsided. She remains on ethionamide. Curettings of the right-sided abscess showed poorly-formed and ill-defined granulomata.

Case 2. A 5-year-old girl from Cardiff presented in January 1978 with a right-sided submandibular swelling and erythema nodosum, She had had a dental extraction 6 months earlier. However, *x*-rays of the mandible and chest were normal. The Mantoux test with 1 TU PPD was strongly positive. The swelling which was an enlarged lymph gland was totally removed (Mr J. Lari). Fortuitum group organisms resistant to all antibiotics except ethionamide, gentamicin, and amikacin were grown. The wound healed and the swelling has not recurred despite the patient being managed without antibiotics. ESR has fallen from 70 mm in the 1st hour and her erythema nodosum has resolved.

Lipid analysis of the two strains showed that one (Case 2) was identical with *M. fortuitum* NCTC 10394 while the other (Case 1) had a slightly different lipid pattern (Marks and Szulga, 1965).

Discussion

Children are constantly exposed to opportunist mycobacteria present in the environment. The organisms most likely to cause cervical adenitis are either *Mycobacterium avium* or *Mycobacterium intracellulare* species, but the presentation of these two children shows that *M. fortuitum* and other species must also be considered. Fortuitum group mycobacteria have been cultured from the sputum of approximately 25% of Welsh miners without immediate illness appearing to result (Jenkins and Marks, 1971), and the organisms must therefore be common. In Case 1 there was no apparent portal of entry; the dental extraction was probably significant with Case 2.

The high degree of resistance of the organism to antibiotics presents difficulties in the management as ethionamide is the only oral medication to which these mycobacteria are sensitive. Case 2 was managed without antibiotics as the gland was totally removed, but the widespread tissue involvement in Case 1 warranted chemotherapy.

We thank Professor O. P. Gray, Dr C. M. Weaver, and Mr J. Lari for permission to publish these cases.

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Progressive hypogammaglobulinaemia in a child born to a mother with Hodgkin's disease

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SUMMARY A young woman developed Hodgkin's disease (nodular sclerosis) in pregnancy and gave birth to a boy who developed common variable immunodeficiency. Initially there was normal IgG with low IgA and IgM, and antibody deficiency. IgG levels fell progressively over 4 years. Cellular immunity was normal. We suggest that this is a further family with immune deficiency presenting with common variable immunodeficiency and lymphoid malignancy.

The association of immunodeficiency with lymphoid malignancy has been reported. We report an unusual combination in a family: a young woman developed Hodgkin's disease in the 3rd trimester of pregnancy and gave birth to a boy who was found later to have common variable immunodeficiency. The father and elder child are normal.

Case histories

The mother. The mother's past medical history was uneventful until her appendix was removed for acute appendicitis at 28 years; during convalescence she developed infective hepatitis.

She noted enlarged cervical lymph nodes during her normal 2nd pregnancy at age 29. A month after confinement she developed a large liver and spleen. A lymph node biopsy showed Hodgkin's disease (nodular sclerosis). She also had lymphopenia ($0\cdot38 \times 10^9/l$). She was treated with radiotherapy and chemotherapy but died 4 years later after a generalised herpes zoster infection.

Lymphocyte counts during remission were often $<1\cdot5 \times 10^9/l$ and usually $<1\cdot0 \times 10^9/l$. No other tests of immunological function were done.

The child. Her son was born normally at term weighing 3·23 kg. He was bottle fed. Growth and development in infancy were normal. He received 3 doses of triple antigen (diphtheria/pertussis/tetanus) and oral polio vaccine during the 1st year of life, and a booster at 18 months. Since then he has had chicken pox and mumps. He has had recurrent nasal discharge, fever, nocturnal cough, occasional wheezing and exertional dyspnoea, intermittent diarrhoea, and two attacks of pneumonia, associated with neutrophil leucocytosis.

At age 5½, he developed herpes zoster. Apart from mild superficial scarring, there were no sequelae. Serum immunoglobulin concentrations were IgG 6·0–6·2 g/l, IgA 0·12 and $<0\cdot10$ g/l. IgM was not detectable. Finger clubbing, a prominent sternum, and persistent coarse adventitial sounds over the right middle lobe were noted. Tonsils and adenoids were very small. He had no lymphadenopathy or enlargement of liver or spleen. *X*-ray showed chronic inflammatory changes in the right upper and lower lobes suggesting bronchiectasis.

At age 6 years, haemoglobin was 11·2 to 12·4 g/dl, with WBC $10\cdot7$ to $12\cdot4 \times 10^9/l$, neutrophils 62%, lymphocytes 33%, monocytes 3%, eosinophils 2%. The absolute lymphocyte count was approximately $4\cdot0 \times 10^9/l$, small lymphocytes 42%, medium lymphocytes 44%, large lymphocytes 14%. Tests of immunity are shown in the Table.

The neutrophil NBT test showed 3% positive cells

Table *Immunological investigations at age 6 years*

Skin tests for delayed hypersensitivity (48 hours)			
Mumps		5 mm	
Streptodornase-streptokinase 60 units		2 mm	
Trichophyton 0·5%		2 mm	
Candida 0·1 and 1% (1)		0 mm	
0·5% (2)		3 mm	
DNCB 2 mg		Negative	
1 mg (after 2 months)		Positive	
Lymphocyte markers			*Normal range*
E-rosettes	29% to 74%		60% to 70%
Surface Ig	17%		10% to 20%
Lymphocyte transformation (counts/min)			
Phytohaemagglutinin	46 000		70–90 000
Pokeweed mitogen	16–50 000		30–50 000
Immunoglobulins			
Serum IgG 6·9 g/l			
IgA not detected			
IgM not detected			
IgE 220/ng/l			

in the resting state, and 72% after latex phagocytosis.

The saliva contained IgG 0·16 g/l and IgA 0·5 g/l. IgM was not present, but free secretory component was detected. The serum IgG showed a reversal of the normal 2:1 kappa to lambda ratio, and was short on immunoelectrophoresis. No antibodies to milk products were present. No antibody was detected to rubella, measles, cytomegalovirus, varicella, mumps, polio type 2, or pertussis. Antinuclear factor was negative.

The blood group was O Rh (D) positive. No anti-A or anti-B was present. The HLA type was A1, A3, B5, B7. The direct antiglobulin test was negative. The bone marrow contained 30% lymphocytes, mainly small forms. No plasma cells were seen in over 1000 cells.

An inguinal node biopsy was taken after a booster dose of diphtheria/pertussis/tetanus into the anterior surface of the right thigh. The node was small and dissected with difficulty. There was little surrounding fibrosis. Cortical lymphoid tissue was sparse with very poor follicle formation and no reacting centres. The paracortical area was normally cellular. Macrophages were present in the peripheral sinuses.

Total haemolytic complement was normal, with normal C1 inhibitor and C1q. C3 was 0·85 g/l and C4 0·3 g/l. No virus was isolated from faeces, but adenovirus type 7 was isolated from a sputum sample on one occasion. Bacterial cultures of sputum grew *Haemophilus influenzae*. On a fat intake of 50 g/day for 3 days the faeces contained 4·5 g fat, i.e. 97% absorption.

Regular postural drainage and injections of immunoglobulin were started.

After a loading dose of 5 days' gammaglobulin, the serum IgG levels rose by the expected amount to 8·5 g/l, but on weekly maintenance, levels have progressively declined by approximately 1·0 g/l per year and have remained at 3·0–4·0 g/l during the last year with continued maintenance. IgA and IgM have not shown any significant changes. IgG was present in the saliva at first, but later became undetectable. There has been no change in the salivary IgA deficiency.

During 4 years of observation, sputum production, chest rales, and finger clubbing have regressed considerably. The chest *x*-ray is now normal. There has been intermittent alopecia areata, and a traumatic synovitis of the hip.

He is growing normally and doing well at school.

Discussion

The patient's immunodeficiency, with normal IgG, deficient IgA and IgM, and antibody deficiency, was at first similar to the case of Giedion and Scheidegger (1957), but without the profound defect of cellular immunity. However, IgG levels fell progressively during treatment with gammaglobulin, and salivary IgG also became undetectable. Skin tests showed positive but weak delayed hypersensitivity, and no conclusive defect of cellular immunity could be shown. B-cells were normal or raised, whereas in sex-linked gammaglobulinaemia they are usually reduced (Cooper and Lawton, 1972). Such patients are now grouped under common variable immunodeficiency. Although the progressive fall of IgG is unusual, it might be found in a larger number of cases if investigations were made early enough. An alternative explanation is that this IgG without detectable antibody activity has been suppressed by replacement with normal antibody.

The alopecia was attributed to trichitillomania, as he has been observed to pull his hair; but it may be a further example of the alopecia associated with hypogammaglobulinaemia described by Ipp and Gelfand (1976).

The mother's disease was histologically nodular sclerosis, the common type of Hodgkin's disease in young women. Lymphopenia is a common feature of Hodgkin's disease. However, Hodgkin's disease in pregnancy is not normally associated with illness in the baby. Poliwoda *et al.* (1967), in an extensive review, reported that 151 of 162 children born to mothers with Hodgkin's disease were normal. Six were stillborn and 10 died within a few hours or before they were three. Follow-up of such children has concentrated on the development of Hodgkin's disease, and not on immunodeficiency. However, these authors noted that one mother had two boys who both died, one with pneumonia and the other with obscure pyrexia and collapse, which could indicate a familial defect of immunity.

We do not attribute our patient's illness to his mother's illness, but there is a well-known association between immunological abnormality and malignancy. Several families have been described with a high incidence of Hodgkin's disease or lymphoma and immunological defect (Potolsky *et al.*, 1971; Buehler *et al.*, 1975). There must be a genetic basis for this combination of disorders in some families, although the occurrence of Hodgkin's disease in husband and wife (Mazar and Straus, 1951) suggests an environmental cause in others. In our case we believe that one genetic defect of immunity has predisposed to malignancy and immunological deficiency.

We thank Dr R. A. Thompson for immunoglobulin estimations and for supplying replacement gammaglobulin, and Dr S. Kumar for tests of lymphocyte markers. Miss V. Rawlinson kindly measured serum complement.

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Intrapartum sensitisation of human infants to the Rhesus-D antigen

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SUMMARY A study is reported of the numbers of nonimmunoglobulin-bearing lymphocytes specifically binding to Rhesus-D positive erythrocytes in the blood of Rhesus-dd infants born to either Rhesus-dd or Rhesus-Dd mothers, at birth and at 6 months of age. There was a significant increase in the number of such antigen-binding cells by age 6 months in babies born to Rhesus-Dd mothers. It is concluded that the Rhesus-negative offspring of Rhesus-positive mothers may be sensitised against the Rhesus-D antigen at birth and that protection of such female infants by the injection of antiRhesus-D antibody should be considered.

The human infant at birth is capable of humoral antibody production against specific antigens. Although these responses are almost confined to immunoglobulin M (IgM) production, small amounts of immunoglobulin G (IgG) can be detected. Immune responses to most antigens require T-lymphocyte help and therefore the presence of specifically reacting T-lymphocytes. The response to the Rhesus-D (Rh-D) antigen is thought to be of this kind.

Since the introduction of treatment with pooled antiRh-D antiserum for Rh-dd mothers postnatally, the incidence of haemolytic disease of the newborn has fallen dramatically. A few new patients are still found, usually ascribed either to the injection or infusion of Rh-incompatible blood or to a failure in treatment with antiRh-D antiserum (Woodrow, 1974). Some studies have suggested, intriguingly, that the birth of a Rh-dd infant to a Rh-Dd mother could lead to intrapartum sensitisation of the offspring, whose latent sensitivity might be reactivated many years later, during the gestation of a Rh-D-positive fetus. Ramos de Almeida and Rosado (1972) found that the incidence of rhesus isoimmunisation by birth rank was dependent upon the grandmaternal Rh blood group, while Taylor (1967) and Hindemann (1973) suggest that sensitisation against Rh-D in infancy may be a significant event.

Some Rh-dd male infants, the offspring of either Rh-dd or Rh-Dd mothers, were selected by the Rh blood group and the ability of their peripheral blood lymphocytes to bind to Rh-D-positive erythrocytes at birth, and at 6 months, was studied.

Materials and methods

Blood samples were obtained from infants via the umbilical cord at birth and by venepuncture from the same infants at 6 months. The cells were purified by density centrifugation (Böyum, 1968) and washed 3 times in Eagle's minimal essential medium buffered with hepes (MEM-hepes). Indicator erythrocytes were either washed in MEM-hepes 3 times before use, or were first treated with a subagglutinating dose of $F(ab')_2$ (Nisonof *et al.*, 1960) antiRh-D antiserum and then washed 3 times in MEM-hepes. Both preparations were made as 1% suspensions in MEM-hepes. The indicator erythrocytes* had been screened for a battery of red cell antigens and known to be positive only for Rh-D, although the presence of other blood group antigens could not be completely excluded.

Equal 50 μl volumes of the lymphocyte suspension, at $2 \cdot 5 \times 10^9$/l (2500/mm^3), and either indicator erythrocytes or indicator erythrocytes previously treated with antiRh-D antiserum, were mixed, centrifuged at 250 *g* for 7 min at room temperature, and incubated at 37°C for 30 min. 50 μl of MEM-hepes containing fluorescein di-acetate (Bodmer *et al.*, 1967) was added, and the numbers of fluorescent rosetted lymphocytes counted under a Leitz Ortholux fluorescent microscope. Control studies, in which lymphocytes had been pretreated with a $F(ab')_2$ antihuman immunoglobulin antiserum, showed that about 5% of rosettes were inhibited in this way, so that most antigen-binding cells (ABC) were non-immunoglobulin-bearing and therefore were probably T-lymphocytes.

Results and discussion

The results in the Table show the numbers of Rh-D-specific ABC detected per 10^6 lymphocytes. The values are derived by subtracting the numbers of rosettes formed after treatment of indicator erythrocytes with $F(ab')_2$ antiRh-D antiserum from the number of rosettes formed without erythrocyte pretreatment, leading to a number of negative values. Although no circulating ABC binding Rh-D antigen were found in cord blood at birth in either group of babies, by age 6 months 6 of 10 infants born to Rh-Dd mothers showed significant numbers of ABC and 2 more infants in the same group showed a smaller rise. Only 2 infants showed no increase in ABC. Three of 12 infants born to Rh-dd mothers demonstrated a small rise in ABC.

Table *Rhesus D antigen-specific rosettes per 10^6 cells formed by cord blood and peripheral blood lymphocytes from Rhesus D-negative infants of Rhesus D-positive and Rhesus D-negative mothers at birth and 6 months of age*

Sample pair	*Rosettes at birth*		*Rosettes at 6 months*	
	Mother Rh-positive	*Mother Rh-negative*	*Mother Rh-positive*	*Mother Rh-negative*
1	−1	−3	291	31
2	4	−2	42	−7
3	3	2	59	−6
4	−2	−4	312	42
5	0	2	218	−4
6	−2	5	125	−6
7	2	−3	−11	6
8	−2	1	149	−4
9	3	5	5	15
10	−3	−2	140	3
11	—	−3	—	−3
12	—	0	—	−4
Probability of difference between groups (Whitney-Mann)	Not significant		Significant at 2% level	

Values for both groups were compared by a Mann-Whitney U test (Mann and Whitney, 1947), which confirmed the similarity between the two groups at birth, but showed a difference, significant at the 2% level, between the two groups at 6 months. These results support the clinical evidence of the effect of the grand-maternal Rh blood group on the incidence of haemolytic disease of the newborn and provide evidence for the intrapartum sensitisation of Rh-dd newborn infants against the Rh-D antigen by transplacental haemorrhage from their Rh-Dd mothers. It may be that, if there is to be a reduction in the small number of mothers where the injection of antiRh-D antibody 'fails' to protect against Rh isoimmunisation, consideration should be given to the protection of Rh-dd infant girls born to Rh-Dd mothers by injection of antiRh-D antibody.

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Fetal growth and parental consanguinity

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SUMMARY Anthropometric measurements made on 322 newborn infants in South India were related to parental consanguinity. Uncle-niece and first-cousin marriages were common and the average coefficient of inbreeding was as high as 0·0329. The measurements (weight, length, head circumference, and triceps and subscapular skinfold thicknesses) of the uncle-niece groups (52 infants) were smaller than those of the first-cousin group (61 infants) which in turn were smaller than the nonconsanguineous group (196 infants). Statistical significance ($P<0 \cdot 01$) was only recorded between the weights of the three groups (means 2650·4, 2794·1, and 2833·8 g) and between the lengths of the uncle-niece group and the nonconsanguineous group (means 46·92 and 47·79 cm). There were no social class or residential differences between the groups. We conclude that there are likely to be recessive genes present in the population, slightly retarding fetal growth.

There are probably more consanguineous marriages in South India than in any other large nonisolated population in the world. Uncle-niece and first-cousin marriages are favoured for a variety of cultural reasons, including keeping property in the family. In the course of a study to assess the effect of maternal nutrition on infant anthropometric measurements (Sibert *et al.*, 1978), we thought it valuable to assess the effect of parental consanguinity on fetal growth.

Material and methods

Mothers and their babies were studied at two hospitals in Vellore, Tamil Nadu, South India: the Christian Medical College Hospital and the Government Pentland Hospital. All singleton infants over 37 weeks' gestation born on unselected days were studied during the period August to October 1977. As information on gestation was inaccurate in a significant number, all infants were assessed by the method of Parkin *et al.* (1976). All but 8 of them were >39 weeks' gestation. None of the mothers smoked.

Interns from the Child Health Department assisted with Tamil translation. Information was collected on the relationship between the parents. Information was also collected on the social class of the father, whether the parents paid for the care, and whether the family lived in an urban or rural area. Birthweights of the infants were recorded by midwives on beam scales. Anthropometric measurements were made by one of us (J.R.S.) within 36 hours of birth. Crown-to-heel length was measured by Cardiff neonatometer, and occipito-frontal head circumference by paper tape measure. Infant skinfold thickness was measured by a Holtain caliper (reading to 0·1 mm) at the left triceps and subscapular sites using the methods of Oakley *et al.* (1977).

In the course of the study one stillborn child of first-cousin parents with a form of achondrogenesis was noted but not included in the study. One living microcephalic child of uncle-niece parents was included.

Results

322 infants were studied. The relationship of their parents is shown in Table 1. Over 39% of the children had consanguineous parents. The average coefficient of inbreeding was 0·0329. Of particular note was the

Table 1 *Relationship of the parents of infants*

	No.	*Proportion of population* (P_1)	*Inbreeding coefficient* (F_1)
Uncle-niece	52	0·162	0·125
Cousin			
First	61	0·189	0·0625
First once removed	5	0·016	0·0313
Second	6	0·019	0·0156
Third	2	0·006	0·0039
All consanguineous	126	0·391	
Nonconsanguineous	196	0·608	

Average inbreeding coefficient ($\Sigma P_1 F_1$) = 0·0329

large percentage (16·2%) of uncle-niece marriages. There were no significant differences between the nonconsanguineous and consanguineous groups in social class of the father, whether the parents paid for the care, or whether the parents lived in an urban or rural area.

The means and SDs of the anthropometric measurements of the groups of infants are shown in Table 2. The anthropometric measurements (weight, length, head circumference, and triceps and subscapular skinfold thicknesses) of the consanguineous group as a whole were smaller than the nonconsanguineous group. Nevertheless the weight of the infant was the only parameter in which the differences reached significance ($t = 2{\cdot}11$, $P<0{\cdot}05$). Looking at the consanguineous group in greater detail the measurements of the uncle-niece group were smaller than the first-cousin group and the measurements of this group, in turn, were smaller than the nonconsanguineous group. Significant differences were only shown between the weight of these groups ($P<0{\cdot}01$) and between the length of the uncle-niece group compared with the nonconsanguineous group ($P<0{\cdot}01$).

Discussion

Our study shows that consanguinity contributes to interuterine growth retardation. Studies in Vellore (Rao and Inbaraj, 1977) showed small but significant increases in perinatal mortality with consanguinity. Decreased fetal growth may be one of the mechanisms for this.

Previous studies on birthweight and consanguinity have shown similar findings to ours with small but usually significant changes. Morton (1958), studying Japanese infants, found mean birthweights of 3074 and 3046 g for his unrelated and first-cousin groups. Similar Japanese data were analysed by Slatis and Hoene (1961) and Schork (1964). Fried and Davies (1974), studying the Moroccan-Jewish community in Jerusalem, found the birthweights of infants with uncle-niece parents were lower (mean 3371 g) than those of unrelated parents (mean 3469 g).

Our work, taken in conjunction with these previous studies, suggests that there are recessive genes with a slightly retarding effect on fetal growth present in the general population. Although the existence of recessive genes causing major effects on growth are well known, there is no evidence that they are widely distributed, at least in South India.

Infectious diseases and malnutrition are the main health problems in South India and the effects of consanguinity are relatively small, taking the population as a whole. Nevertheless we have seen many tragedies in consanguineous marriages with as diverse recessively inherited conditions as thalassaemia, Niemann-Pick disease, and spinal muscular atrophy. We believe that the reduction in the number of consanguineous marriages in South India, particularly those between uncle and niece, will become increasingly important as the burden of infectious disease and malnutrition is brought under control.

We thank the British Paediatric Association and the H. J. Heinz company for funding the fellowship of J.R.S. We also thank Professor S. X. Charles, Head Department of Obstetrics and Gynaecology, Christian Medical College, and Dr K. Kalyaram, District Medical Officer, North Arcot District, Tamil Nadu, for letting us study their patients, and Dr D. P. Davies and Mr R. Newcombe for their help.

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Table 2 *Anthropometric measurements of groups of infants, arranged by consanguinity of the parents*

Anthropometric measurement	*Uncle-niece*		*First-cousin*		*All consanguineous (n=126)*		*All nonconsanguineous (n=196)*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Weight (g)	2650·4	371·2	2794·1	498·2	2731·	435·1	2833·8	406·9
Length (cm)	46·92	2·07	47·65	2·43	47·36	2·22	47·79	2·16
Head circumference (cm)	32·67	1·31	33·42	1·51	33·10	1·43	33·35	1·60
Triceps skinfold (mm)	3·51	0·71	3·55	0·73	3·57	0·72	3·58	0·70
Subscapular skinfold (mm)	3·36	0·67	3·46	0·65	3·42	0·66	3·51	0·74

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European Society for Paediatric Nephrology

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Amyloid nephropathy in familial Mediterranean fever. D. Zemer, M. Pras, and H. Boichis. Tel-Hashomer. Israel.
Familial Mediterranean fever, common among Sephardic Israelis, usually starts in childhood, with a 90% mortality by age 40, mainly from amyloid nephropathy. Of 1000 patients given daily colchicine since 1972, none of the 968 who had no proteinuria initially has developed amyloid. Of 32 nephropathic patients treated for 2 years, the condition of 14 has improved, 6 remain static, and 12 have deteriorated.

Nephronophthisis (N): a review. A. Drukker. Jerusalem, Israel.
Nephronophthisis (N) and medullary cystic disease are probably one disease. Genetic differences remain unclear because criteria for the heterozygous state are lacking. N is not a primary cystic but a renal interstitial disease. Morphological and functional evidence favour a primary tubulopathy, perhaps proximal. A co-operative effort is needed to evaluate the origin of N.

Ocular abnormalities in nephronophthisis (N). Th. Lennert, K. Scharer, and M. Brandis. Berlin, Heidelberg, and Hannover, FRG.
10 of 20 cases of nephronophthisis (N) showed ocular abnormalities; 5 had tapeto-retinal degeneration, 3 nystagmus, 2 amblyopia, 1 cataract, 1 strabismus, 1 myopia, and 1 hypertensive retinopathy. Autosomal dominant inherited medullar cystic disease (MCD) is not associated with eye abnormalities. N is indistinguishable from Senior-Loken syndrome but may be different from MCD.

Epidemiology of kidney diseases in Finland in 1970-74. R. Lappi. Helsinki, Finland.
All patients treated in hospital in 1970-74 were analysed; 3 patients per 100 000 population had urinary disease; 12% were < 15 years of age, and 6% <5 years. 90% of all patients had pyelonephritis or urological disease, but nephrosis, nephritis, and congenital malformations were more common in children.

Risk factors for cardiovascular diseases in children. F. Dorner, A. Spahr, R. Gautier, and J. P. Guignard. Lausanne and Sion, Switzerland.
1000 children aged 5, 7, and 10 years and 200 parents were examined. Obese children had higher blood pressures (BPs) than controls; no correlation between hypercholesterolaemia and BP was found. BPs were higher in parents of children with raised diastolic BPs. No severe hypertension was found; 5·2% of children had proteinuria and 1·9% had haematuria. Routine screening is unjustified but obese children and those with a family history should be examined.

'Compensatory hypertrophy' of renal size in children with chronic pyelonephritis and unilateral renal damage. I. Claësson, B. Jacobsson, and J. Winberg. Gothenburg, Sweden.
26 randomly selected children with unilateral renal scarring from chronic pyelonephritis were followed up for 11 years. 16 had compensatory hypertrophy of the contralateral kidney but ipsilateral hypertrophy after damage was rare. Estimates of total renal area from radiographs suggested that the hypertrophy compensated for much of the renal damage and this compensatory growth accelerated in adolescence.

Syndrome of inappropriate ADH secretion in mechanically-ventilated newborn infants. J. Nutman, E. Wilunsky, and S. H. Reisner. Petah Tiqva, Israel.
Three of 106 infants admitted to the neonatal intensive care nursery over 6 months had the syndrome of inappropriate ADH secretion diagnosed from hyponatraemia, weight gain, and highly concentrated urine. All were on mechanical ventilation, onset was rapid, and deep coma occurred in one infant. Fluid restriction and sodium replacement led to rapid improvement.

Cellular localisation and time course activity of alkaline and acid phosphatases in the nephrotic rat kidney. J. J. Helwig, C. Bollack, and J. Geisert, Strasbourg, France.
Nephrotic syndrome was induced by puromycin injection, proteinuria occurred on day 5 and was maximal on day 9. Alkaline phosphatase in tubules and medulla rose on day 1 and was at its maximum on day 5, but was unchanged in glomeruli and cortex. Acid phosphatase was greater in glomeruli on day 1 but rose on days 6 and 7 in glomeruli and

tubules. It is not clear whether these changes correlate with the renal disease or are a clinical effect of puromycin.

Renal cystic disease. J. Bernstein. Michigan, USA.
Infantile polycystic disease (IPCD) and adult polycystic disease (APCD) may present at birth but can be distinguished clinically, radiologically, morphologically, and genetically. The hallmark of IPCD is medullary ductal ectasia, and in APCD there is irregular cyst distribution with severe glomerular involvement; cysts are commonly surrounded by smooth muscle fibres. Cysts may be secondary manifestations of heritable metabolic defects rather than inherent themselves. Tuberose sclerosis is an important differential diagnosis in a child with cystic disease.

Podocyte degeneration in glomerular disease. J. Churg and E. Grishman. New York, USA.
Degeneration of glomerular epithelial cell podocytes is common in many renal diseases. Either the original cell or a new cell can regenerate, adding in a haphazard fashion to the thickness of the basement membrane. Similar changes are seen in animals given puromycin or diacetylbenzidine, suggesting that podocyte damage is of toxic origin; impairment of capillary circulation may be a factor. The denudation of the basement membrane may account for the proteinuria.

Recent advances in congenital nephrosis of Finnish type (CNF). J. Rapola. Helsinki, Finland.
The incidence of congenital nephrosis of Finnish type (CNF) in Finland is 12 per million population per year and 6-8 new cases occur annually. Amniocentesis was performed on 23 'at risk' pregnancies, and in 7 patients, raised levels of amniotic alpha fetoprotein were found. Electron microscopical examination of kidneys from the aborted fetus confirmed the diagnosis in each case. Glomerular basement membranes in CNF show a decrease in collagen and 3-hydroxyproline of collagen, but the significance of these changes is not yet understood.

Prognosis of haemolytic-uraemia syndrome in children. M. F. Gagnadoux and R. Habib. Paris, France.
Between 1967 and 1976, 71 children with haemolytic-uraemia syndrome were studied. The incidence of terminal renal failure was 12% in infants and 54% in older children. Renal biopsy within one month of onset and a year later in 22 children showed that prognosis was related to the number of glomeruli affected and whether the child had cortical necrosis; the development of severe hypertension correlated with the severity of vascular changes. The biopsy appearances were unique with progression to sclerosis of affected glomeruli.

Incidence, primary renal disease, and growth of children less than 5 years of age treated by regular dialysis and transplant. K. Scharer. Heidelberg, FRG.
87 children less than 5 years at start of treatment were registered with the EDTA (European Dialysis and Transplant Association) in 1977. Survival at one year was 90% and at 2 years it was 77%, similar to older children. Nearly half the children lived in France and accounted for 10% of children treated there. Haemolytic-uraemia syndrome and cortical necrosis were important causes of renal failure. Growth was similar to that of older children.

Amino-acid metabolism and growth in infants with chronic renal failure. C. Giordano. Naples, Italy.
Daily weight gain was studied in infants with chronic renal failure on low-protein diets with supplements of different essential amino-acids (EAAs) and keto-acids. Marked improvement was demonstrated especially with EAAs but the formula of the EAA supplement used was critical.

Carbohydrate and lipid metabolism in chronic renal failure. C. Chantler. London, UK.
Energy metabolism is disturbed in renal failure with failure of normal glucose metabolism leading to potential cellular energy deficiency, protein malnutrition, and hyperlipidaemia. Low-protein diets with amino-acid supplements theoretically may ameliorate this but must be supplemented with energy; polyunsaturated fats should be used to reduce carbohydrate intake if hyperlipidaemia occurs.

Survey of the experience of the French paediatric units with dialysis and transplant programmes in children under 5 years of age. M. Broyer. Paris, France.
Since 1969, 32 children (4 months–4½ years) have been accepted for dialysis and transplant programmes in 6 paediatric units. Chronic haemodialysis (CHD) was generally performed with radial or humeral internal fistulae. Chronic peritoneal dialysis (CPD) was used alternately with CHD when vascular access was not available. 11 cadaver kidney transplants were done. 11 children have died, 9 are living with kidney transplants, 10 remain on CHD, and 2 on CPD at home. Survival was 74%, 70%, and 62% at 1, 2, and 3 years.

Renal transplantation in children aged 1 to 5 years. S. M. Mauer. Minneapolis, USA.
Results of renal transplants in young children are sufficiently good compared with children of other ages for treatment to be offered to such children.

Incidence of chronic renal faliure in Swedish children. I. Helin and J. Winberg. Malmo, Stockholm, Sweden.
To be published in full elsewhere.

Dialysis bone disease in childhood: treatment with 25 hydroxycholecalciferol (25OHD3). R. Dumas, J-Cl. Luciani, and P. Meunier. Montpellier, France.
Five children on haemodialysis were treated with 25 OHD_3. Plasma calcium rose excessively in one child; growth velocity, plasma parathyroid hormone levels, and histological lesions of osteitis fibrosa cystica were unchanged. The osteomalacia present in one child improved and in 2 children a decrease in trabecular bone volume was observed.

Effects of various protein diets on growth, renal function, and survival of uraemic rats. I. Salusky, C. Kleinknecht, and M. Broyer. Paris, France.
Low-protein diet has been incriminated in growth failure in ureamia. In uraemic rats, high-protein diets (37%) and (27%) had deleterious effects on growth and survival, and led to progression to renal failure, compared with a diet limited to minimal requirements (14%). It is important to avoid any protein excess in chronic uraemia.

Effect of anabolic steroids on growth in boys with chronic renal failure on haemodialysis. J. E. Carter, J. Burke, M. El-Bishti, R. Counahan, V. Wass, N. Dalton, and C. Chantler. London, UK.
Nine boys were treated with oxandrolone; in one the drug was stopped because of a rise in liver enzymes. Height velocity improved significantly and the children grew more rapidly than the advance in bone age. Intracellular water (cell mass) increased. Improvement in glucose tolerance and plasma branch chain amino-acids was observed.

Delayed puberty in males with chronic renal failure. P. Saenger, J. Ferraris, L. S. Levine, S. Pang, M. I. New, and J. E. Lewy. New York, USA.
31 boys aged 11 to 20 years were studied. Testosterone, dehydrotestosterone, and luteinising hormone levels were appropriate for pubertal status, suggesting normal Leydig cell function and activity of 5 α reductase enzyme. FSH levels were raised, suggesting damage to germinal eptihelium but they became normal after successful transplants.

Serum ferritin (SF) concentrations in children with chronic renal failure. D. E. Muller-Wiefel, E. Wolf, D. Schönberg, and K. Schärer. Heidelberg, FRG.
Serum ferritin (SF) levels were determined in 32 children with chronic renal failure, 9 children on dialysis, 8 children with transplants, and 25 controls. The level of SF was raised in all groups compared with controls. SF should be measured before starting iron treatment in children with renal failure because few of them are iron deficient.

Echocardiographic investigation of cardiac action during haemodialysis of children. J. R. Pfefferkorn, L. Diekmann, and U. Schulten-Baumer. Munster, FRG.
12 children on regular haemodialysis were examined. All showed increases in interventricular septum and posterior left ventricular wall due to myocardial hypertrophy. End diastolic diameter of left ventricle was increased, suggesting dilatation, but this decreased significantly during dialysis with fluid removal.

Dialysis and transplantation results in Europe 1977: review of the data from the paediatric registry of the EDTA. R. A. Donckerwolcke, C. Chantler, F. P. Brunner, H. J. Gurland, R. A. Hathway, C. Jacobs, H. Brygner, N. H. Selwood, and A. J. Wing. Holland, UK, Switzerland, FRG, France, and Sweden.
Results were published in *Proceedings of the European Dialysis and Transplant Association*, Volume 15, (1978) Pitmans Medical: London.

Mediation and effects of intrarenal fibrin deposition. P. F. Naish. Stoke, UK.
Intrarenal fibrin deposition may result from primary glomerular inflammation, or microvascular damage with or without intravascular coagulation. Defibrination is associated with protection from glomerular damage. Studies in nephrotoxic nephritis and endotoxin infusion in rabbits indicate the central role of neutrophils in fibrin deposition. Studies of neutrophils, platelets, and coagulation in patients may enable rational treatments to be developed.

Platelets and glomerulonephritis. J. S. Cameron. London, UK.
Platelets are important in the pathogenesis of glomerular damage from chronic soluble complex disease; antiplatelet agents may have a role in treatment but more studies using new tests of platelet function—such as serotonin levels—are needed to confirm this.

Combination therapy for mesangiocapillary nephritis in childhood. S. J. Chapman, J. S. Cameron, C. Chantler, and D. R. Turner. London, UK.
11 children with mesangiocapillary nephritis were treated with prednisolone, azothioprine, heparin, or warfarin; 7 children had a significant rise in glomerular filtration rate (GFR), in 2 the declining GFR stabilised, and 2 in terminal renal failure did

not improve. In 2 children there was a rapid fall in GFR after withdrawal of immunosuppression.

Pathogenesis of focal glomerular hyalinosis and sclerosis. J. D. Elema, M. S. Schilthuis, and J. Grond. Groningen, The Netherlands.
From clinico-pathology observations in children with a variety of glomerular diseases and from experimental studies in rats, it is suggested that focal segmental hyalinosis and sclerosis is a nonspecific lesion. Local haemodynamic factors (pressure, flow) and changes related to the existence of nephrosis (hyperlipidemia, hypercoagulability) are pathogenetically involved although to different extents in different circumstances.

Immunological studies in the haemolytic-uraemia syndrome. L. Monnens, M. de Jong, P. van Muster, and J. Molenaar. Nymegen, Amsterdam, The Netherlands. To be published elsewhere.

Renal function and biopsy studies in patients with IgA and poststreptococcal glomerulonephritis. A one-year follow-up. T. Linne, A. Aperia, and O. Broberger. Stockholm, Sweden.
The renal functional changes of IgA and poststreptococcal glomerulonephritis were similar. GFR was depressed initially but became normal during the first months of the disease. The natriuretic response to an isotonic saline infusion was low in the early course of the disease, and took longer to become normal than GFR.

Deficiency of the second component of complement (C2D) with membranoproliferative glomerulonephritis. Recurrence after transplant. C. Loirat, C. Blum, M. Broyer, and M. Levy. Paris, France.
Membranoproliferative glomerulonephritis with subendothelial deposits was observed in a C2D boy without systemic disease. Immunofluorescence showed IgC, C1q, and C4 as granular deposits along capillary walls and within the mesangium. C3 was also deposited along capillary walls. The clinical course was severe. Recurrence of the glomerular lesions was observed 9 months after transplant.

Nonfamilial recurrent haematuria. L. Callis, M. Carreras, E. Vilaplana, and F. Castello. Barcelona, Spain.
Five girls aged 5–11 years had recurrent haematuria. Family history, renal function, complement levels, hearing, and renal biopsy evaluation by light microscopy and immunofluorescence were normal. Electron microscopical examination showed deposits within the basement membrane or thickening of the basement membrane with layering. The latter changes, present in 2 children, may represent a variant of Alport's syndrome.

Nephropathy in cyanotic congenital heart disease. J. P. Dommergues, M. Levy, M. C. Gubler, R. Habib, and V. Courtecuisse. Paris, France.
Three patients with congenital heart disease had a low glomerular filtration rate, haematuria, and proteinuria. Renal biopsy showed mesangial proliferation, and a double contour thickening of basement membrane due to a heterogenous deposit on the endothelial surface. Immunofluorescence was negative. Renal function improved after successful surgery and the glomerular changes disappeared in one case.

Role of circulating immune complexes (IC) in renal disease. R. J. Levinsky. London, UK.
Immune complexes (IC) differ in immunoglobulin class, subclass, size, complement binding, and antigen, and these differences account for the different results of the several tests used for detecting them. Size of IC is important in the pathogenicity of IC in lupus nephritis; the nonlocalisation of IC in steroid-sensitive nephrosis is probably due to the failure of the IC to bind complement. IgA IC are found in Henoch-Schoenlein disease but nephritis only occurs if IgG IC are present as well. The production of different IC may depend on the genetic differences of the host's immune response to antigen and may underlie the susceptibility to disease.

Complement profiles and C3 nephritic factor-like activity (C3NeF-L) in children presenting with acute glomerulonephritis or membranoproliferative glomerulonephritis (MPGN). M. Levy, M. Sich, E. Pirotsky, and R. Habib. Paris, France.
Activation of the classical pathway was demonstrated in acute glomerulonephritis (34 patients) and membranoproliferative glomerulonephritis (MPGN) type 1 (20 patients) with C3NeF-L (*Clinical Immunology and Immunopathology*, 1978, **10,** 477) in 9 and 7 respectively of these patients. Conversely, activation of the alternative pathway was documented in 13 patients with MPGN type 11, 10 of whom had C3NeF-L.

Complement activating factor (C3AF) in membranoproliferative glomerulonephritis. E. J. Lewis, B. G. Bartlow, and J. L. Roberts. Chicago, USA.
A factor capable of activating C3 (C3AF) by the alternative pathway was isolated by cryoprecipitation from a patient with type 1 membranoproliferative glomerulonephritis. Unlike C3 nephritic factor C3AF is not an IgG; it is suggested that C3AF activates C3 by interaction with $\beta 1H$ leading to increased activity of the 'amplification feedback loop'.

Kinetics of glomerular visceral epithelial cell phagocytosis of macromolecular aggregates from the lamina rara externa of the glomerular basement membrane. Z. Sharon and M. M. Schwartz. Illinois, USA.

The sequential intravenous administration of protamine and heparin results in aggregation and deposition of protamine-heparin aggregates (PHAgs) in the lamina rara externa of the glomerular basement membrane. Experiments in rats confirmed that removal of HPAgs is accomplished by epithelial cell phagocytosis by first-order kinetics unrelated to GFR. Epithelial cell removal of immune aggregates may be important in acute poststreptococcal nephritis and perhaps in other glomerular lesions with subepithelial deposition of immune complexes.

Alternate-day v. intermittent prednisone in frequently relapsing nephrotic syndrome. J. Brodehl and H. P. Krohn. Hannover, FRG.

A prospective study was performed in 48 children with frequently relapsing nephrotic syndrome to compare alternate-day prednisone (23 children) (35 mg/m^2 per 48h) with intermittent prednisone (25 children) (40 mg/m^2 in 3/7 days) during 6-months' treatment. Results show that alternate-day prednisone is significantly more effective than equal amounts of intermittent prednisone for preventing patients from relapsing and for reducing the number of relapses.

Spontaneous remission and delayed therapy in steroid-sensitive nephrotic syndrome. R. J. Postlethwaite, I. B. Houston, and P. C. Powell. Manchester. UK.

To be published in full elsewhere.

Nephrotic syndrome. Value of new methods in kidney biopsy specimens. K. Kuehn, M. Brandis, R. Castelucci, and E. Reale. Hannover, Germany.

Ultrastructural investigation by scanning electron-microscopy and freeze-fractured preparations of renal biopsies from children with minimal change nephropathy showed swelling of capillary epithelium, and widening and loss of peripheral foot processes, without real fusion.

Allergo-immunologic testing in children with nephrotic syndrome due to minimal change (MC) and focal glomerular sclerosis (FGS). D. E. Muller-Wiefel, U. Wahn, V. Lenhard, and W. Rebien. Heidelberg, FRG.

Atopic history score and serum IgE levels were similar in minimal change (MC), focal glomerular sclerosis (FGS), and controls, but 4 children with MC had high levels. The proportion of positive prick tests and increased IgE antibodies was similar in the three groups but lymphocyte stimulation was depressed in MC, with intermediate results in FGS. One child with atopic MC, out of 3 desensitised to grass pollen, entered a stable remission, Allergic mechanisms play a role in only a few children with MC.

Nephrotic syndrome associated with tubular disorders in 5 children. Ph. Barthe and F. Bouissou. Toulouse, France.

Five children with steroid-resistant nephrotic syndrome developed mixed tubular acidosis (5/5), hypokalaemia (4/5), glycosuria (5/5), hypophosphataemia (2/5), aminoaciduria (2/5), and tubular proteinuria (2/5). Progression to renal failure occurred and repeat biopsy showed focal glomerular sclerosis.

Distal renal tubular acidosis (DRTA) in 23 infants and children. M. Dechaux, M. Broyer, G. Lenoir, and P. Guesry. Paris, France.

23 infants and children with primary distal renal tubular acidosis (DTRA) were studied; one had bicarbonate wasting, 3 had no systemic acidosis. Deafness was noted in 5. Dehydration and vomiting were early signs, nephrocalcinosis was common with hypercalaemia. Concentrating capacity was reduced in 15 children. Growth improved with treatment. Familial factors were present in 7 children. DTRA is not a homogenous disorder.

Adolescent cystinosis. Case report and review of the literature. G. Knopfle, H-P Weber, and E. Harms. Bonn, Heidelberg, FRG.

Cystinosis was diagnosed in a 13-year-old boy with a Fanconi's syndrome and a glomerular filtration rate of 34 ml/min per 1·73m^2. Growth and development were normal. Progression to renal failure occurred over 5 years. Adolescent cystinosis is associated with glomerular proteinuria, lower intracellular cystine than in the infantile form, and slower progression.

Physical chemical basis of urinary stone disease. W. G. Robertson, M. Peacock, R. W. Marshall, and B. E. C. Nordin. Leeds, UK.

Abnormal crystalluria leading to stone disease results from imbalance between saturation of urine and inhibitory activity which prevents large aggregates; pH, calcium oxalate, acid mucopolysaccharide, and uric acid are important factors in this balance. The relative contribution of these risk factors enables the probability of stone formation in an individual to be calculated.

Idiopathic hypercalciuria (IH)—an old enigma. U.A. Liberman. Petah Tiqva, Israel.

There appear to be 4 varieties of idiopathic hypercalciuria (IH): (1) increased intestinal calcium absorption, (2) decreased tubular calcium reabsorption, (3) normocalcaemic hyperparathyroidism, and (4) decreased tubular phosphate reabsorption. The aetiology of these forms of IH remains obscure.

Idiopathic hypercalciuria in childhood: clinical and metabolic studies. M. Tieder, H. Stark, and R. Shainkin-Kerstenbaum. Beer-Sheba, Israel.

Compared with 10 controls, 3 children with IH demonstrated evidence of: (1) increased intestinal calcium absorption, (2) decreased parathyroid (PTH) and increased calcitonin (CT) activity, (3) low plasma phosphate due to low TmP/GFR (phosphate reabsorption). These suggest that low TmP/GFR is primary, causing low Pp, which stimulates 1.25 $(OH)_2$ vitamin D production and increased Ca absorption. This, with resulting low PTH and high CT, causes hypercalciuria.

Hypercalciuria (HC), nephrocalcinosis, and nephrolithiasis in metabolic disorders. O. Mehls, F. Manz, and H. Schmidt. Heidelberg, FRG.

Hypercalciuria (HC) secondary to hypercalcaemia is seen with vitamin D intoxication. HC due to failure of proximal tubular reabsorption occurs in the Fanconi's syndrome in association with decreased sodium reabsorption; magnesium supplements to correct hypomagnesaemia may cause HC by competing for reabsorption. In renal tubular acidosis HC is secondary to the metabolic acidosis. Hyperoxaluria may cause nephrolithiasis and 5 of 70 children with phenylketonuria (PKU) developed stones; hyperoxaluria occurs in some children with PKU and occasionally with tyrosinosis.

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Archives of Disease in Childhood, 1979, **54**, 326–327

Correspondence

Kawasaki disease

Sir,

I read with interest the letter of Morgan and Lynch (*Archives*, 1978, **53**, 916), and should like to report 2 more white children in the UK—one Welsh and one English.

A 6-year-old boy from Anglesey was admitted in June 1978; 2 weeks previously he had developed fever and a blotchy red rash over the face with red macules on the trunk. He was seen by his doctor, diagnosed as having tonsillitis and scarlet fever, and given a 5-day course of ampicillin. His condition did not improve. On the 12th and 13th days of his illness (two days before admission) he developed peripheral limb pain, particularly around fingers, wrists, ankles, and toes. He was febrile, 38·6°C. There was bilateral cervical lymphadenopathy. The throat was inflamed. There was a grade-1 systolic murmur. Swelling of the fingers, hands, and wrists was noted. At this stage no firm diagnosis was made, but 3 days later prominent tongue papillae, oedema proceeding to skin peeling of the hands and feet, and a high ESR (100 mm in the 1st hour) were noted, and the diagnosis of mucocutaneous lymph node syndrome (MLNS) was made. Hb was 10·6 g/dl. Other investigations gave normal results: white blood count, urine analysis and culture, ASO, throat swab, chest *x*-ray, Paul Bunnell test, blood culture, and ECG.

After 18 days' illness his temperature remitted. The skin continued flaking from the periphery for another 2 weeks, but otherwise he was well, and has remained so for the subsequent 5 months.

A 3½-year-old girl from Merseyside on holiday in Wales presented with a 4-day history of fever for which a doctor had prescribed ampicillin. She had experienced a sore throat, a slight cough, and a few loose stools. The day before admission she had developed an erythematous rash with peeling on the face, trunk, and nappy area.

On examination she had a fever of 39·5°C. There was cervical lymphadenopathy, and an erythematous rash on the face, upper trunk, and nappy areas, with peeling around the nappy area. The tongue papillae were unusually and markedly prominent. The throat and ear drums were injected. There was no heart murmur. Hb was 10·8 g/dl, ESR 106 mm in the 1st hour, urine trace albumin, nil sugar, microscopy and culture negative, CSF normal, throat swab negative, ASO 605 units, blood culture negative, plasma Na 128 mmol/l, K 4·8 mmol/l, Cl 98 mmol/l, plasma urea 20 mg/100 ml (3·3 mmol/l), ECG normal, chest *x*-ray normal, C3 complement 1·16 g/l (raised).

Initially the diagnosis was thought to lie between toxic epidermolysis, due to a staphylococcal toxin, and MLNS. Treatment was started with IV fucidin to no effect, the child remaining febrile and ill. On the 8th day of illness, oedema of the extremities developed and peripheral joint arthralgia. On the 9th day the child was transferred to Alder Hey Children's Hospital, Liverpool, under the care of Professor Harris to be closer to her home. The oedema and arthralgia of the periphery subsided quickly, but the skin of the periphery continued to peel for 2 or 3 weeks. She subsequently recovered completely (4 months later).

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Acquired toxoplasmosis and acute hemisyndrome in childhood

Sir,

In an article (*Archives*, 1978, **53**, 414) McNicholl and Flynn reported on 9 cases of acquired toxoplasmosis in childhood, 2 of whom contracted an acute hemisyndrome with persisting sequelae. We observed a similar case in a 5-year-old boy who gradually developed hemiplegia over 24 hours (9–10 December 1977). The boy had been treated with penicillin for an otitis media during the preceeding week. On admission he had a complete left-sided hemiparesis, but had neither lymphoglandular enlargement nor chorioretinitis. An acute right carotid angiography, isotope, and computerised axial tomography (CAT) scans were negative. A repeat CAT scan 6 months later was still normal. CSF findings were inconclusive. Improvement was initially rapid but subtotal. Currently, one year later, only a slight left-sided dysfunction and spasticity remains.

The patient is a farmer's boy and had been playing with his cat. Toxoplasma antibody titres in the patient and cat were as shown in the Table:

1978	*5 January*	*February*		*31 May*	*7 August*
		7	*14*		
Patient					
Immunofluorescence					
IgM	128	64			
IgG	1024	1024			
Complement fixation	128	128		32	32
Dye test	1000	4000		500	500
Cat					
Immunofluorescence			1024		
Dye test			≥250		

As both a significant increase in dye test titre and toxoplasma antibodies of the IgM-class were demonstrable, the findings indicated that the patient had ongoing toxoplasmosis. It appears most likely that the disease was acquired from the cat which had high serum levels of toxoplasma antibodies. Trimethoprim-sulphafurazole treatment (6 February–15 May) may have contributed to the rather rapid fall in antibody titres.

Acquired toxoplasmosis has occasionally been identified in acute hemiplegia in childhood (Sabin, 1941; Hedenström *et al.*, 1958; Lelong *et al.*, 1960). Isler (1971) reported only one case of toxoplasmosis (a 12-year-old boy with a left-sided parietal lobe syndrome with a complete restitution) among 116 acute hemisyndromes in children.

Acquired toxoplasmosis may thus occasionally be the cause of an acute childhood hemiparesis. A focal encephalitis may not be envisaged on the CAT scan and the diagnosis should accordingly be looked for by serological and microbiological methods.

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Hedenström, G., Huldt, G., and Lagercrantz, R. (1958). Toxoplasmosis studies. *Acta paediatrica*, **47**, 329–330.

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Sabin, A. B. (1941). Toxoplasmic infections in children. *Journal of the American Medical Association*, **116**, 801–807.

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Dose of clonidine in alternating hemiplegia

Sir,

My fellow authors and I wish to point out that in our paper (*Archives*, 1978, **53**, 656–659) there is an error (page 658) in the dose of clonidine given to one of the patients. The dose quoted should have read 2·5 μg/kg per day (not milligrams).

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Archives of Disease in Childhood, 1979, **54**, 328

Book reviews

Separation and Special Care Baby Units. Clinics in Developmental Medicine No. 68. Edited by F. S. W. Brimblecombe, M. P. M. Richards, and N. R. C. Roberton. (Pp. 113; illustrated + tables. £6.00 hardback.) Spastics International/ Heinemann: London. 1978.

This monograph, edited by two paediatricians and a social psychologist, reviews the evidence on the effects of early separation on children and their parents and discusses admission and discharge policies of special care baby units. Several studies of babies in such units are presented. The project described in most detail is the study of parental visiting of babies admitted to the Exeter unit. It illustrates well how social circumstances and distance influence frequency of visiting. Even in this unit, committed to encouragement of visitors, some parents never came to see their babies. A study from Queen Charlotte's Hospital demonstrates how little contact babies in incubators have with any adult. Unfortunately the number of term babies on lying-in wards observed for comparison was so small that no conclusions about differences can be drawn. A contribution from a paediatrician and nurse describes how efficient medical care can be combined with a sympathetic approach to parents, and introduces the idea of an intermediate care area which does not entail separation. Statistics presented from Exeter show that only a small proportion of handicapped 5-year-old children had passed through the special care baby unit.

While not disputing the need to increase and improve intensive care facilities, the editors criticise the over-enthusiastic admission of babies 'for observation' because of minor symptoms or because their entries into the world were not completely normal. The argument against such unnecessary separation is convincing. It is futile to expect such a practice to reduce mortality or morbidity figures. The experiences of the Cambridge unit demonstrate how the trend towards increased admission rates can be safely reversed. For about 10% of newborns some separation will be inevitable. Much can be done to promote contact between these babies and their families. The special care all babies need is the caring of their parents.

MARGARET A. LYNCH

Shorter notices

Bibliography of Infant Foods and Nutrition 1938–1977. By J. O. Henderson, S. M. Collins, L. L. Muller, and B. S. Harrap. (Pp. 322. Australian $16.00, paperback.) Commonwealth Scientific and Industrial Research Organization: Australia. 1978.

This bibliography gives the authors, titles, references, and abstract numbers of a broad selection of scientific publications from 1938 to mid-1977, mainly from Dairy Science Abstracts (DSA), Nutrition Abstracts and Reviews (NAR), Food Science and Technology Abstracts (FSTA), and Agricola SDI Service (AGRIC) (formerly) CAIN). Papers included emphasise aspects of infant foods in relation to nutrition, but those on specialised aspects of medicine are excluded.

Host Defenses in the Human Neonate. Monographs in Neonatology Series. By M. E. Miller. (Pp. 123; illustrated + tables. £8.10, hardback.) Grune and Stratton: New York. 1978.

This monograph by a respected research worker is concise, readable, and, for the paediatrician, illuminating. The author sets out to examine the interactions of t various components of inflammatory a immune responses, instead of dealing wi the various systems of immunity isolation. He succeeds brilliantly, a provides important food for thought those concerned in the treatment neonatal infection.

Paediatrics. Second edition. By J. Apl (Pp. 453; illustrated. £4.95, limp cove Ballière Tindall: London. 1979.

The first edition of this limp-cover textbook was favourably reviewed *Archives*, 1974, **49**, 163. The format of t second edition is the same and it remai an excellent and readable introduction the concepts and facts of paediatrics the undergraduate student. It has stay reasonably small and reasonably priced.

Rehabilitation of Arm Amputees a Limb-Deficient Children. By Elizab Robertson. (Pp. 209; illustrated + tabl £8.50 hardback.) Ballière Tindall: Lond 1978.

This excellent book embodies unrivalled experience of the former he occupational therapist to the childre unit, Queen Mary's Hospital, Roehampton, and is predominantly about lin deficient children. Every occupatio therapist trying to help even one s child deserves a copy. It is totally practi in approach and in it such things discussed as parental attitudes, as well training, prosthetics, and gadgetry. O gratitude to Elizabeth Robertson sharing her wisdom, and to Act Research for the Crippled Child helping to make it available, lavis illustrated and in hardback, at a barg price!

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The Journal of the British Paediatric Association

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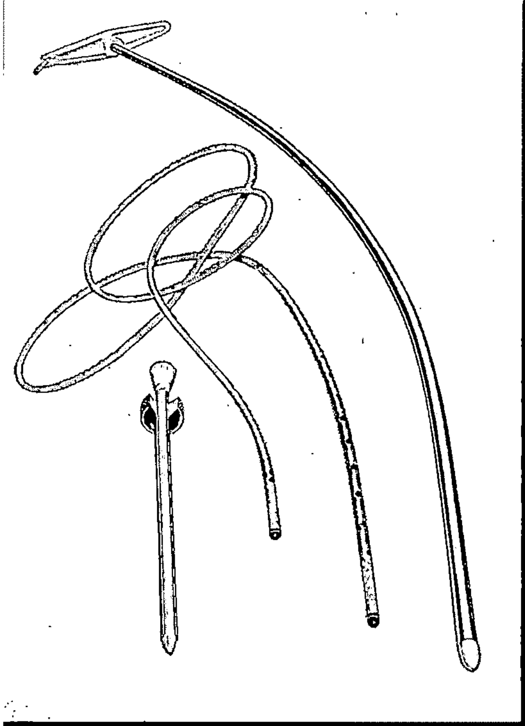

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Archives of Disease in Childhood, 1979, **54**, 329–330

Annotation

Diagnosis of malignant hyperphenylalaninaemia

The occurrence of progressive cerebral degeneration in some patients with phenylketonuria (PKU) despite early and adequate dietary control of serum phenylalanine is now well established. The clinical syndrome was clearly described by Smith *et al.*[1] At a conference held in Lausanne, June 1977,[2] of groups of people who have written papers on the subject, it was agreed that malignant hyperphenylalaninaemia (MHPA) was the best term to describe such cases. Readers seeking additional documentation of the facts should refer to the report of that meeting.[3]

MHPA is present in between 1 and 3% of babies with positive results to Guthrie tests, including some babies with serum phenylalanine levels lower than would customarily be treated with diet.[4] All cases so far recognised suffer a deficiency of tetrahydrobiopterin (BH_4), the cofactor of phenylalanine hydroxylase, tyrosine hydroxylase, and tryptophan hydroxylase. Deficient production of the neurotransmitter products of tyrosine and tryptophan is regarded as the cause of the neurological effects[5] and the gratifying results reported in Lausanne of treatment with L-dopa and 5-hydroxytryptophan support this contention.[6] Two classes of basic defect have been found: deficiency of dihydropteridine reductase (DHPR) which is required for recycling BH_4[7] and defective synthesis of biopterin.[7,8,9] Paediatricians treating PKU are faced with the need to identify patients with MHPA in order to treat them effectively and also to allow confident dietary treatment for the remaining 97–99% of patients with PKU. Patients with MHPA can then be further classified by DHPR assay on cultured skin fibroblasts (or on liver biopsy), by phenylalanine hydroxylase assay (on liver biopsy), and in future by assay of specific enzymes concerned in BH_4 synthesis.

The time has now come to introduce systematic testing of all babies with persistently raised levels of serum phenylalanine by measuring the response to a single oral dose of BH_4 (2 mg/kg). This test should be performed as part of the initial work before diet is begun, and the serum phenylalanine level should be measured before and 6 hours after the dose.[4] MHPA is recognised by a fall of serum phenylalanine to normal levels; patients with classical PKU show no response.

The advantage of this method is that the result can be known immediately, before diet is started, and no other laboratory test is needed. Lack of pure BH_4 is the one problem at present, but if there were a demand from several clinics it could soon be made available. Several research laboratories are already synthesising BH_4 and the quantities needed are not great.

We showed the effect of intravenous BH_4 in a patient who was initially thought to have partial DHPR deficiency,[10] but was later found to have severe DHPR deficiency.[4] Comparable response in patients with deficient BH_4 synthesis was expected and has now been shown by Schaub *et al.* who also showed that oral administration was as effective as parenteral.[9]

Another useful approach to the recognition of MHPA is the study of urinary pteridines. The simplest method is to estimate dihydroxanthopterin (XH_2) in urine. DHPR deficiency causes excessive levels of XH_2 in the urine.[11] The levels overlap those found in patients with classical PKU before treatment, and clear distinction requires retesting after dietary control when levels are still high in DHPR deficiency but have fallen to normal in classical PKU. Urinary XH_2 should be abnormally low in patients with defects of BH_4 synthesis. One may expect to find some precursors of BH_4 in the urine in these cases. Doubtless high performance liquid chromatography of urine may give a diagnostic profile in such cases, but findings in DHPR deficiency can overlap those in classical PKU (before treatment). These approaches to diagnosis necessitate setting up new laboratory methods and there are likely to be delays in diagnosis because response to dietary treatment may be critical in some cases. Some of the chemicals measured are unstable in urine (in serum) and careful treatment of samples is necessary.

For all these reasons we feel convinced that the BH_4 load test will become established as the best method for identifying cases of MHPA promptly and efficiently. Many different approaches are then possible in evaluating these few patients with MHPA to reach a final diagnosis, but proof of the enzyme defect is likely to remain the final arbiter.

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Archives of Disease in Childhood, 1979, **54**, 331–338

Neonatal form of dystrophia myotonica

Five cases in preterm babies and a review of earlier reports

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Departments of Paediatrics and Neurology, Sophia Children's Hospital, and Academic Hospital, Erasmus University, Rotterdam

SUMMARY Five preterm babies with the neonatal form of dystrophia myotonica are reported. In addition to the generally accepted signs and symptoms of the disease, two other features were present in these patients; oedema was notable in all 5 babies and 4 had unexplained haematomas. It is suggested that premature birth may be a result of severe involvement and that prematurity further aggravates the symptoms.

The neonatal form of dystrophia myotonica is now recognised as a clinical entity which is quite different from the adult form of the disease (Vanier, 1960). The clinical picture is characteristic and consists of extreme hypotonia and generalised muscle atrophy, combined with polyhydramnios, insufficient respiratory activity after birth, joint deformities, and facial diplegia with a 'tent-shaped' mouth. The adult form of the disease, however, comprises myotonia and localised muscle atrophy with cataracts, frontal baldness, and testicular atrophy.

In a 7-month period, 5 preterm babies in whom the diagnosis of dystrophia myotonica could be made were admitted to our neonatal intensive care unit. We describe these babies, report two hitherto unstressed features of this disease, and review previous reports on the neonatal form of dystrophia myotonica.

Case reports

Case 1. A baby girl was delivered by caesarean section at another hospital at 30 weeks' gestation because of abruptio placentae. The pregnancy had been complicated by polyhydramnios. After delivery the baby made no spontaneous attempt to breathe and was ventilated by mask until the arrival of our neonatal transport team. She was intubated and given intermittent positive pressure ventilation (IPPV).

On admission she weighed 1840 g and was hypotonic (Fig. 1a) with a 'tented' upper lip (Fig. 1b),

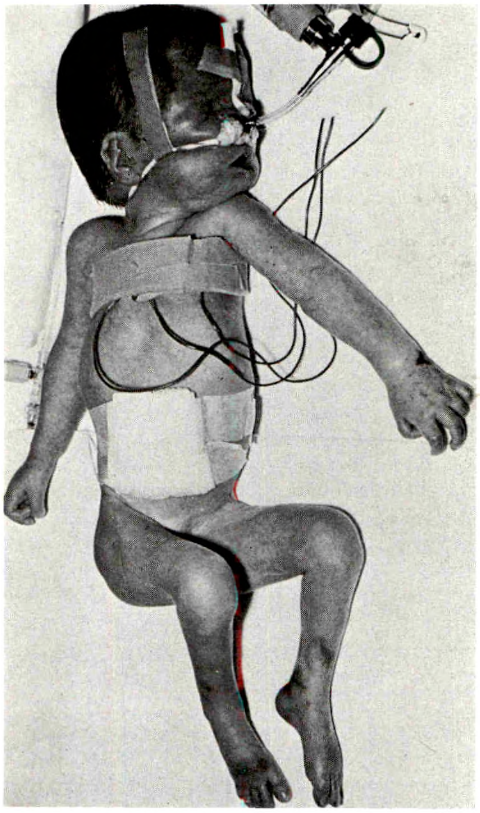

Fig. 1a *Characteristic posture of the premature infant with dystrophia myotonica. Hypotonia of the shoulder girdle can be seen with muscle atrophy in the legs and flexion contractures of the hips and talipes equinovarus.*

Sophia Children's Hospital and Neonatal Unit, Rotterdam, The Netherlands

R. G. PEARSE, consultant paediatrician
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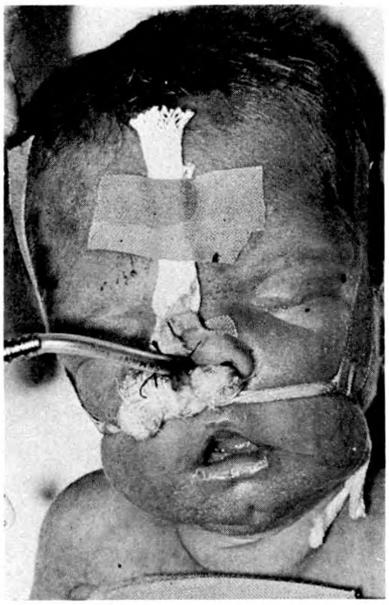

Fig. 1b *Typical facies of dystrophia myotonica in the newborn. The 'tent shaped' mouth and oedema are obvious. (See also Figs 3, 5, 7, and 9.)*

facial diplegia, and absent sucking and gag reflexes. She had unexplained haematomas of the labia minora (Fig. 1c), upper thighs, and arms, and pronounced oedema of the head and limbs. There were flexion contractures of the hips with talipes equinovarus, and the muscles of the arms and legs appeared atrophic (Fig. 1a). She lost 450 g (24% of birthweight) in the first 5 days in spite of intravenous feeding. This was thought to be due to the loss of oedema fluid. There was little change in her clinical condition and she died on day 19 without a diagnosis other than perinatal asphyxia. Necropsy examination gave no cause for her death. The diagnosis was made when the similarity was recognised between this baby and a baby admitted one month later (Case 2) in whom the diagnosis of dystrophia myotonica had been made. Subsequent examination of the mother of Case 1 confirmed the diagnosis.

The mother

A 33-year-old woman who had no spontaneous complaints. However on direct questioning she admitted to having had 'stiff hands' during this and previous pregnancies. On examination she had the classic findings of moderately severe dystrophia myotonica with a myopathic facies (Fig. 2), weakness of distal limb muscles, and myotonia of grip. She has two healthy children now aged 3 and 6 years. They have both been examined and have no symptoms or signs of dystrophia myotonica, but EMG and slit-lamp examination could not be performed. Her third pregnancy ended at 28 weeks with the delivery of a

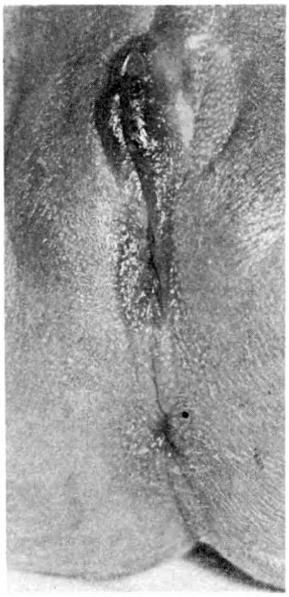

Fig. 1c *Haematoma of the labia minora.*

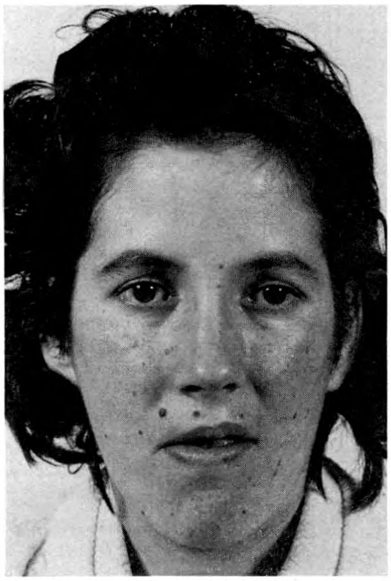

Fig. 2 *Mother of Case 1. Typical facies of dystrophia myotonica. Atrophy of the temporalis and masseter muscles can be seen, also ptosis and the typical smile of facial muscle weakness. (See also Figs 4, 6, 8, and 10.)*

1640 g baby who died soon after birth from respiratory insufficiency, supposedly secondary to prematurity. Four of the mother's five sisters have been shown to have dystrophia myotonica.

Case 2. A baby girl was born at home by spontaneous vaginal delivery at 36 weeks' gestation after a pregnancy complicated by polyhydramnios. She failed to breathe adequately after birth and was transferred to our hospital. On admission she weighed 2820 g and was cyanotic, hypotonic, hypothermic (34·4°C), and markedly oedematous. She had a 'tent-shaped' mouth (Fig. 3), facial diplegia, atrophy of limb muscles, and haematomas of the dorsal and palmar aspects of both hands for which no explanation could be found. Coagulation studies were normal. A differential diagnosis of cerebral haemorrhage or muscle disease was made. Lumbar puncture produced freely blood-stained CSF and CAT scan showed subarachnoid, interstitial, and intraventricular haemorrhage. A detailed family history taken at this time led to the diagnosis of dystrophia myotonica and subsequent examination of the mother confirmed this. During the first few days after birth the baby had episodes of apnoea and bradycardia of varying duration from which she spontaneously recovered. Thereafter the respiration improved and she began to move spontaneously. She still had difficulty in drinking and swallowing on discharge from hospital at age 7½ weeks when she weighed 3240 g. Her maximum weight loss in the first week was 480 g (17% of birthweight). She learned to sit unsupported and to roll at age 8 months. She is now 11 months and can stand with support, although she is unable to pull herself up to a sitting or standing position.

The mother

A 23-year-old woman who was unaware that she had dystrophia myotonica, although on questioning she had had myotonic symptoms in the hands since age 13. On examination she had mild but typical features of dystrophia myotonica (Fig. 4), including the characteristic cataracts and the EMG. Her father and brother were also found to have dystrophia myotonica. This was her first pregnancy.

Case 3. A baby girl was delivered by the breech at 33 weeks' gestation after a pregnancy complicated by polyhydramnios. She did not breathe spontaneously and during resuscitation attempts at introducing a nasogastric tube were unsuccessful, so that she was initially diagnosed as having oesophageal atresia. She was intubated and given IPPV, and then transferred to our hospital.

On admission she weighed 1350 g and was extremely hypotonic and oedematous. She made no spontaneous movements and was areflexic. She had generalised muscle atrophy with bilateral talipes equinovarus and flexion contractures of the hands and hips. There was a facial diplegia, a 'tent-shaped' mouth (Fig. 5), and haematomas over the limbs and upper thoracic and neck regions. Without IPPV she rapidly became cyanotic even in 100% O_2. There was no evidence of oesophageal atresia and the diagnosis of the neonatal form of dystrophia myotonica was made on the clinical findings, subsequently confirmed when we examined the mother. After 3 days

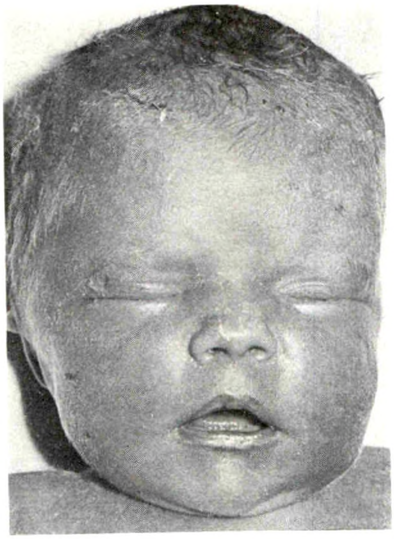

Fig. 3 *Case 2, showing same features as in Fig. 1b.*

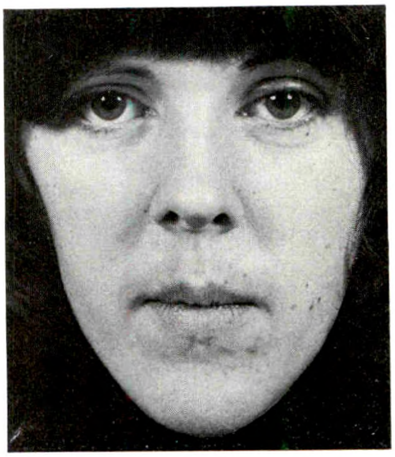

Fig. 4 *Mother of Case 2, showing same features as in Fig. 2.*

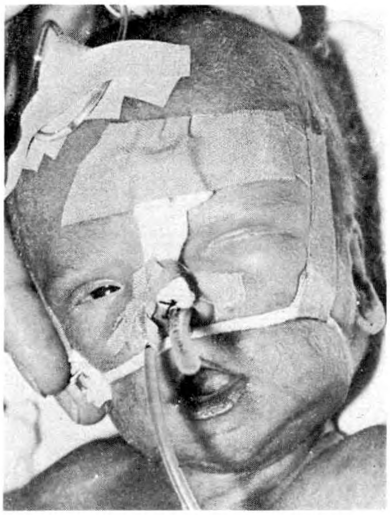

Fig. 5 *Case 3, showing same features as in Fig. 1b.*

on IPPV the baby died. At necropsy examination a subcapsular haematoma of the liver was found, plus the unexpected finding of agenesis of the corpus callosum. A coagulation screen done at age 24 hours was normal. Her maximum weight loss was 200 g (15% of birthweight).

The mother
A 21-year-old woman who had noticed myotonic symptoms since age 6 but, as she was familiar with them from her mother, uncle, and aunt, she had never reported them. She is mentally retarded and has an indistinct nasal speech. On examination she had typical myopathic facies (Fig. 6) and the findings of moderately severe dystrophia myotonica were confirmed by the EMG. This was her first pregnancy.

Case 4. A baby girl was born at another hospital at 34 weeks' gestation after a pregnancy complicated by polyhydramnios (9 litres) and premature contractions which had been treated with ritodrine chloride for one week. She was ventilated with a mask for 15 minutes but then was able to maintain a reasonable colour in 100% O_2. On admission to our hospital she weighed 2000 g and was hypotonic and oedematous. She had the typical facies of the neonatal form of dystrophia myotonica (Fig. 7), the muscles of her arms and legs were atrophic, and her feet were held in plantar flexion. There were haematomas of both legs and feet. Her respiration was inadequate and she was intubated and ventilated for 19 days. She developed congestive cardiac failure secondary to a patent ductus arteriosus which closed spontaneously. She had had difficulty with drinking but was discharged at 10 weeks weighing 3060 g. Her maximum weight loss in the first week was 445 g (22% of birthweight). She is now 7 months old but does not roll or sit. Her head control is poor but is improving.

The mother
A 26-year-old woman who was unaware of her muscle disease, although on direct questioning she

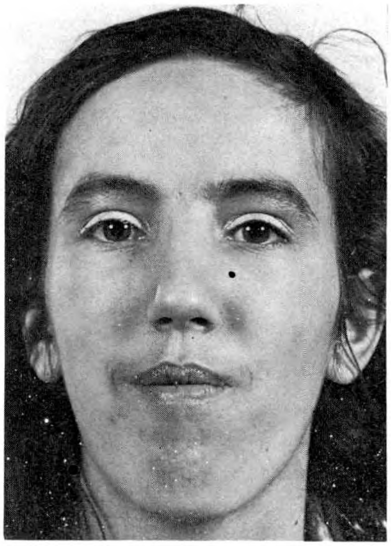

Fig. 6 *Mother of Case 3, showing same features as in Fig. 2.*

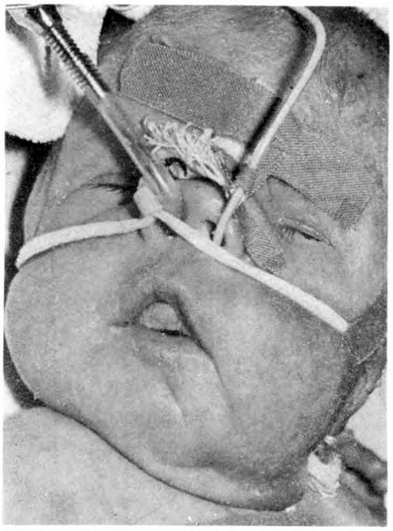

Fig. 7 *Case 4, showing same features as in Fig. 1b.*

had had myotonia of grip since age 18. On examination she had an obvious but mild degree of dystrophia myotonica (Fig. 8) and this was confirmed by the EMG. Her first pregnancy was complicated by polyhydramnios and ended at 33 weeks with the delivery of a baby who was hypotonic and did not breathe, attempts at resuscitation being unsuccessful. The mother's father has subsequently been shown to have a cataract typical of dystrophia myotonica although he has no muscle symptoms.

Case 5. A baby girl was delivered at 30 weeks' gestation at another hospital after a pregnancy complicated by polyhydramnios and a pyrexia of unknown origin just before delivery. The Apgar score was 3 at five minutes. She was intubated and transferred to our hospital on IPPV. On examination she was hypotonic and oedematous with the typical 'tent-shaped' mouth and facial diplegia (Fig. 9). Sucking and swallowing reflexes were absent and no tendon reflexes could be elicited. There were neither haematomas nor joint deformities but muscle atrophy was obvious. She was not weighed on admission but her weight was estimated to be about 2000 g. Her condition improved slowly but she required IPPV for 61 days. The clinical course was complicated by a patent ductus arteriosus which was closed surgically on day 44. She is now 6 months old and is still in hospital with feeding difficulties and recurrent pneumonia. She is hypotonic and is still being partially tube fed. She makes little or no contact.

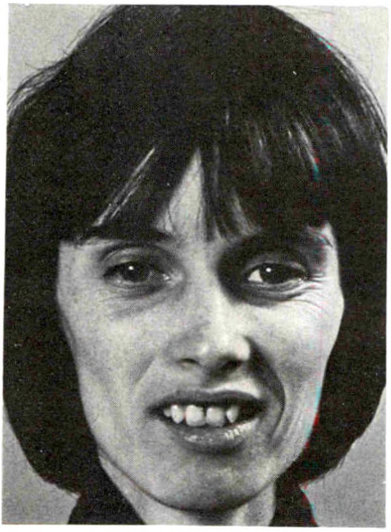

Fig. 8 *Mother of Case 4, showing same features as in Fig. 2.*

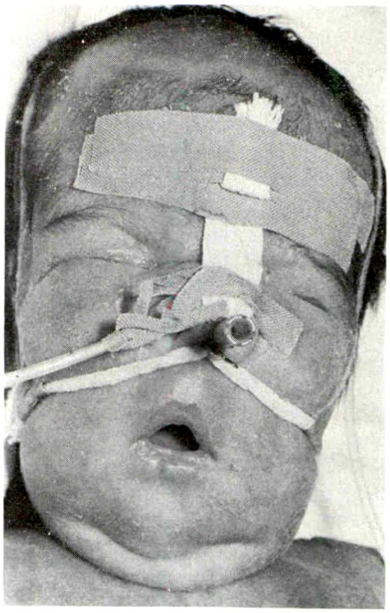

Fig. 9 *Case 5, showing same features as in Fig. 1b.*

The mother

A 37-year-old woman who was examined for dystrophia myotonica 4 months before the delivery because she is the sister of the mother of Case 1. She had had myotonic symptoms in the hands during this and the previous pregnancy although she had never complained of them. On examination she had obvious dystrophia myotonica of mild severity (Fig. 10) with cataracts and the typical EMG.

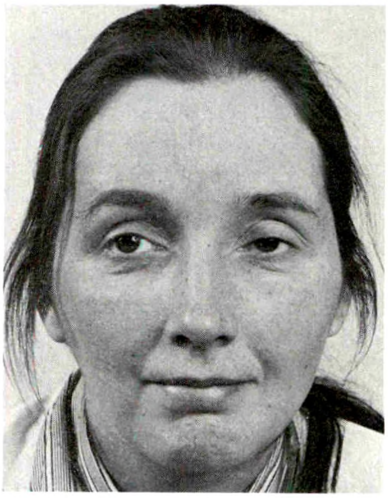

Fig. 10 *Mother of Case 5, showing same features as in Fig. 2.*

She has had two children now aged 11 and 13 years. They have no signs or symptoms of dystrophia myotonica and EMG and slit-lamp examination are normal in both. Her third pregnancy had been complicated by polyhydramnios and ended at 28 weeks with the delivery of a boy who failed to breathe, and died soon after birth.

Discussion

Dystrophia myotonica is a diagnosis which is easily missed in the newborn and is therefore probably not as rare as it would appear. This is supported by the high immediate postnatal mortality in families with dystrophia myotonica (Harper, 1975). The mother of Case 1 and her four affected sisters have between them had 21 babies of whom 8 have died soon after birth. In 5 of these there was documented polyhydramnios, suggesting that these babies died from dystrophia myotonica although the diagnosis was never made.

The individual symptoms of the disease as expressed in the newborn are nonspecific. However their occurrence in a particular combination makes recognition relatively easy. Some of these symptoms can be misleading. Severely affected babies often fail to establish adequate spontaneous respiration after birth. They are therefore diagnosed as having perinatal asphyxia, which may be considered adequate cause for the severe hypotonia seen. This receives apparent support when it is found that the baby also has difficulty with sucking and swallowing. However all these symptoms are an integral part of the neonatal form of dystrophia myotonica.

Harper (1975) described the characteristic features of the disease in newborn babies in his large retrospective study of 70 patients from 54 sibships. These are shown in the Table, together with the features described in 17 patients by other authors and in our series. There are obvious differences in the symptoms reported by Harper in this retrospective study and those reported in the series where the diagnosis was made in the neonatal period. All except one of the babies in Harper's series survived the neonatal period and only about half of them had respiratory difficulties. All the babies who were diagnosed in the neonatal period have had respiratory problems and half of them (11/22) have died.

The Table shows that the most commonly reported symptoms in the group diagnosed in the newborn period are respiratory insufficiency, hypotonia, joint deformities, and facial diplegia. Most of these babies have also had areflexia with muscle weakness and atrophy, and difficulty with sucking and swallowing. The inability to suck and swallow is probably the cause of the polyhydramnios (Dunn and Dierker, 1973) which has been found in all cases in which the quantity of amniotic fluid has been reported.

Table *Reported frequency of various symptoms and signs (where these are given) compared with the incidence in this series*

Symptoms and signs	*70 cases diagnosed retrospectively (Harper, 1975)*	*Reports* of 17 cases diagnosed in neonatal period*	*This study (5 cases)*	*Total cases diagnosed in neonatal period (22)*
Respiratory problems	33/70	17/17	5/5	22/22
IPPV necessary	—	10/17	4/5	14/22
Hypotonia	47/70	17/17	5/5	22/22
Joint deformities	33/70	17/17	3/5	20/22
Facial diplegia	61/70	13/14	5/5	18/19
Areflexia	—	8/10	5/5	13/15
Muscle atrophy	—	4/4	5/5	9/9
Feeding problems	—	13/13	5/5	18/18
Oedema	—	2/2	5/5	7/7
Haematomas	—	—	4/5	4/5
Hydramnios	25/70	8/8	5/5	13/13
Mean birthweight (g)	3200	2900	1800	—
Mean gestational age (weeks)	39·5	39·5	32·6	—
Mortality	1/70	9/17	2/5	11/22
Transmission via mother	66/67	17/17	5/5	22/22
Delayed motor development	60/70	5/5	3/3	8/8

*L'Hirondel *et al.*, 1970; Bell and Smith, 1972; Messer *et al.*, 1973; Aicardi *et al.*, 1974; Bossen *et al.*, 1974; Simpson, 1975; Swift *et al.*, 1975; Sarnat *et al.*, 1976; van der Steeg *et al.*, 1977.

We found that oedema was characteristic in our patients (Figs 1b, 3, 5, 9). The average weight loss in the four babies in whom this was accurately known was 19·5% of birthweight, whereas in our unit it is less than 10% of birthweight for babies of a similar gestational age who receive similar treatment regimens. This weight loss was thought to be largely due to the loss of oedema fluid. Clinically the oedema was most noticeable on the limbs and head, while the trunk appeared relatively spared. The muscle artophy became more evident as the oedema disappeared. Oedema was also noted at birth in the patients reported by L'Hirondel *et al.* (1970) and Messer *et al.* (1973). An explanation for this oedema could be that secondary to reduced fetal movements there is reduction in lymphatic return from the periphery. The disappearance of the oedema in the first few days after birth may be related to the passive movements inherent in the intensive care of sick newborn babies.

A second notable feature in our cases was the existence of haematomas. In 4 of the 5 babies these were located in the skin, and one also had an intracerebral haemorrhage, and another baby a large subcapsular haematoma of the liver. Coagulation studies performed in 2 of the babies were normal. It can perhaps be postulated that these babies are unable to protect themselves against the trauma of delivery due to muscular weakness and hypotonia. However Stern *et al.* (1978) showed that abnormal capillary leakage occurs in the iris of adults with dystrophia myotonica during fluorescein angiography. Microvascular abnormality may thus be an important factor in the formation of haematomas in these babies but has yet to be studied.

The diagnosis of the neonatal form of dystrophia myotonica is essentially clinical. There are no laboratory tests which are diagnostic in the newborn period. Both muscle biopsy and EMG give only supportive evidence and necropsy examination does not provide the diagnosis. If the diagnosis is suspected, it can be confirmed by examining the mother. Although the disease is transmitted as an autosomal dominant, the neonatal form always appears to be transmitted via the mother (Harper and Dyken, 1972). An initially negative family history does not exclude the diagnosis because the mother may be so mildly affected that she may be unaware that she has the disease. The signs which should be particularly sought are the characteristic facies (Figs 2, 4, 6, 8, 10) with facial weakness, hollow temples, myotonia of grip, and percussion myotonia of the thenar eminence. Inability to bury the lower eyelashes when closing the eyes tightly is a useful early sign of the disease in adults. Slit-lamp examination and EMG may be performed to confirm the diagnosis in the mother. Only one of the mothers in our series was known to have dystrophia myotonica at the time of delivery.

The differential diagnosis of the congenital form of dystrophia myotonica includes all the causes of the 'floppy infant' (Dubowitz, 1969). Thus cerebral depression from anoxia, trauma or drugs, spinal cord injury, neonatal myasthenia gravis, Werdnig-Hoffmann's disease, and other congenital myopathies should be considered.

Unlike the reported cases, all the babies in our series were preterm. Sarnat and Silbert (1976) suggested that the symptoms in the neonatal period are due to relative immaturity of muscle tissue. Thus more severe symptoms could be expected in the preterm baby. However, there is probably a spectrum of severity in the intrauterine involvement of babies with dystrophia myotonica, ranging from the fetus who is aborted early in the pregnancy, through the baby who is born preterm and dies soon after birth, to the term and mildly affected baby who survives. Thus the baby born preterm may be both more severely affected and have had less time in which maturation of muscle tissue could take place. As would be expected in severely affected babies, polyhydramnios was present in all of our cases, and was probably one of the factors responsible for the premature delivery. It may be possible to delay delivery with uterine relaxants and by the repeated removal of excess amniotic fluid. This may moderate some of the life-threatening symptoms of the neonatal period by allowing the muscles more time to mature.

Harper and Dyken (1972) suggested that the neonatal form of dystrophia myotonica may be caused by an abnormal factor in the mother's serum which crosses the placenta but only affects babies carrying the abnormal gene. If this is so, then it is clear that it operates from early in pregnancy as our most premature affected infant was of 30 weeks' gestation and she already had joint contractures suggesting that the factor, if present, had been operative for some time.

Difficult ethical problems arise once the diagnosis has been made. If babies with dystrophia myotonica survive the first few weeks then there is a gradual improvement, at first in respiration, followed by improvement in swallowing, and eventually in the hypotonia. Although their development is slower than normal, most of them learn to walk and speak (Harper, 1975). However the long-term prognosis is poor and there is little hope of an independent life due to the combination of mental retardation and muscle weakness. Dyken and Harper (1973) found an average IQ of 56 in 14 patients who had had respiratory symptoms in the neonatal period.

Because the baby fails to breathe adequately immediately after birth, and usually the mother is not known to have dystrophia myotonica, the diagnosis is made when the baby is already being ventilated. We found it difficult to decide whether, and to what extent, we should continue treatment. The prognosis for both mental and physical handicap was discussed with the parents, but in each case they requested that every measure should be taken to keep the baby alive. The shock of hearing that both mother and baby have a serious disease must make a well-judged decision at such an emotional time extremely difficult for the parents.

Antenatal diagnosis could alleviate some of these problems. The gene for dystrophia myotonica is linked to the gene for secretor status and the latter can be determined in saliva and amniotic fluid. However this linkage is only helpful in antenatal diagnosis in about 15% of couples (Schrott *et al.*, 1973).

Until a better technique for antenatal diagnosis becomes available, the only reasonable approach would seem to be to attempt to identify all affected members of families with dystrophia myotonica and to offer genetic advice if appropriate. Recognition of the neonatal form of dystrophia myotonica can lead to the identification of such families and to more timely genetic counselling.

We thank the doctors and nurses involved in the treatment of these patients, the parents and relatives of the babies who co-operated in the family studies, the audio-visual departments of Sophia Children's Hospital and Dijkzigt for the photographs, and Mrs M. de Bruijne for secretarial help.

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A year's experience of the rotavirus syndrome and its association with respiratory illness

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SUMMARY In a hospital study rotavirus was identified in 51% of 152 children with diarrhoea. These patients showed a clinical pattern that was distinct from patients in whom the diarrhoea was associated with bacteria, other viruses, or no pathogens. A respiratory illness was described in 66% of rotavirus patients and usually preceded the gastrointestinal symptoms. Vomiting lasted between one and 3 days and was curtailed by substituting the normal diet with clear fluids. Watery diarrhoea continued for 4 or 5 days, even when rehydration was by the intravenous rather than the oral route. Prolonged diarrhoea was rare. Most children infected with rotavirus were under 2 years of age, but dehydration was most severe in infants aged between 12 and 18 months. A clinician can thus recognise the rotavirus syndrome and expect spontaneous recovery if adequate rehydration is maintained for a critical few days.

The clinical features of patients admitted to hospital with gastroenteritis were studied in north-west London between 1968 and 1970 (Sinha and Tyrrell, 1973). The results showed that there was a distinct nonbacterial, winter epidemic disease which mainly affected children under 2 years and was often associated with symptoms and signs in the respiratory tract. An 'infantile gastroenteritis virus' was predicted and this was soon proved correct. Reports have universally shown that rotavirus particles can be seen in the stools of 15 to 90% of infants with diarrhoea but are absent from the stools of most healthy children. The highest isolation rates have been in temperate climates, particularly in the winter months (Bishop *et al.*, 1974; Davidson *et al.*, 1975; Kapikian *et al.*, 1976; Dupont *et al.*, 1977; Konno *et al.*, 1977; Schoub *et al.*, 1977; Walker-Smith, 1978).

Most observations of the clinical features of rotavirus infection indicate that vomiting is common (Shepherd *et al.*, 1975; Rodriguez *et al.*, 1977; Tallet *et al.*, 1977) and dehydration can be severe (Rodriguez *et al.*, 1977; Tallet *et al.*, 1977). Concurrent respiratory symptoms have been noted in retrospective analysis but have not proved significantly more frequent than in cases where diarrhoea is not associated with rotavirus (Carr *et al.*, 1976; *British Medical Journal*, 1977a; Rodriguez *et al.*, 1977; Tallet *et al.*, 1977). Because of possible omission of relatively mild respiratory symptoms in a predominantly gastrointestinal illness these studies do not show the true incidence or importance of respiratory tract involvement.

The patients in this prospective study lived in the same geographical area as those reported in 1968–70 (Sinha and Tyrrell, 1973). The aims were to define the clinical features of rotavirus infection and to explore the association between respiratory illness and pathogen in infantile gastroenteritis.

Patients and methods

The patients were children admitted to the paediatric or infectious diseases unit of Northwick Park Hospital during a complete year (1977); they had

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passed frequent loose stools for at least 24 hours at some stage of their illness and required replacement of the normal diet with clear fluids. Nearly all children were examined by the same clinician within 24 hours of admission and each day thereafter, and the findings were recorded on a standard form. Stools and throat swabs were collected once from each child as early in the illness as possible. Stools were studied by electron microscopical examination for rotavirus. The stools and throat swabs were cultured for viruses and for pathogenic bacteria. From some children who had signs of respiratory illness, nasopharyngeal secretions were aspirated and material from a plain throat swab was smeared on to a glass slide. These were stored, and 10 specimens were later examined by electron microscopy because virus particles were seen in the corresponding faecal specimens.

Stools for virology were sent immediately to the laboratory or stored at −70°C. A 10% suspension of stool was prepared in nutrient broth containing penicillin, streptomycin, and amphotericin B. The suspension was centrifuged at 2500 *g* for 10 minutes, then the supernatant was centrifuged at 10 000 *g* for 30 minutes at 4°C to remove bacteria. This supernatant was used for electron microscopical examination and for virus isolation tests. For electron microscopy 2 ml of faecal extracts were ultracentrifuged at 100 000 *g* for one hour at 4°C, and the deposit was negatively stained with potassium phosphotungstate using a technique described elsewhere (Flewett *et al.*, 1974). Grids were examined in a Philips EM 300 at a viewing magnification of 28 000.

For viral culture, 0·2 ml of stool suspension was inoculated into 2 tubes of each of 3 types of tissue cultures: human embryonic lung fibroblasts (MRC 5), Ohio HeLa cells, and secondary monkey kidney cells. Inoculated tissue cultures and uninoculated controls were incubated in roller drums at 33°C.

Throat swabs for virus isolation were taken on sterile plain cotton swabs and broken into virus transport medium (nutrient broth with antibiotics). If possible, throat swabs were kept at 4°C until inoculation. Within 2 hours 0·2 ml of the fluid was inoculated into 2 tubes of each of the 3 tissue cultures.

Viruses from both stools and throat swabs were detected by their cytopathic effects. Haemadsorption tests were performed on monkey kidney cells which were inoculated with respiratory specimens. Some adenovirus and enterovirus isolates have not been serotyped. Cultures were incubated for 4 weeks before they were discarded as negative.

Nasopharyngeal secretions were aspirated after injection of 2 ml normal saline into each nostril. This material was ultracentrifuged at 100 000 *g* for one hour. The resulting pellets were fixed in glutaraldehyde and osmium tetroxide buffered solutions, embedded in Spurr resin and sectioned. Sections were stained with uranyl acetate and lead, and examined for virus particles by electron microscopy. Both the nasopharyngeal secretions and the smeared slides from throat swabs were examined by negative staining (Flewett *et al.*, 1974).

For bacteriology fresh stool specimens were plated on to deoxycholate agar and MacConkey's medium, and inoculated into selenite broth. Enteropathogenic *Escherichia coli* were identified using antisera (Central Public Health Laboratory, Colindale) to 15 recognised enteropathogenic types. From April 1977 a selective medium was used to isolate campylobacter species (Skirrow, 1977). Microscopical examination of stool specimens for parasites was performed if there had been diarrhoea for more than 10 days or if the child had recently returned from abroad.

Bacterial throat swabs were taken on sterile serum-coated wool buds and transported in Stewart's medium. They were cultured on blood and chocolate agar. Colonies were identified by standard techniques and all streptococci were grouped serologically.

The completed clinical and microbiological data were punched on to computer cards. Tables and significance tests were produced by computer analysis (Nelder, 1974).

Results

A total of 150 children were studied and 8 were rejected because they did not pass any stools after admission. Two children were admitted twice, but as both were asymptomatic between admissions each illness was considered as a separate episode. Thus 152 episodes of diarrhoea were investigated and these were divided into 5 groups according to the pathogens identified in the faeces (Table 1).

The largest was group 1 containing 74 patients from whom rotavirus was detected, although on tissue culture, 6 of these also showed an adenovirus and 3 an enterovirus.

Table 1 *Results of testing faeces*

Group	*Stool pathogens*	*Patients n=152*	
		No.	*(%)*
1	Rotavirus	74	(49)
2	Pathogenic bacteria	23	(15)
3	Other viruses	26	(17)
4	No pathogens	26	(17)
5	Rotavirus and pathogenic bacteria	3	(2)

Group 2 contained 23 patients with pathogenic bacteria: salmonella 9, shigella 8, enteropathogenic *E. coli* 1, and campylobacter species 5. Of these, one child had *Giardia* on light microscopy and 2 showed an adenovirus, detected by tissue culture.

Group 3 contained 26 patients from whom viruses other than rotavirus were the only pathogens identified. The results of tissue culture were: adenovirus 9, enterovirus 9. Electron microscopical examination showed adenovirus 3, enterovirus 3, astrovirus 1, coronavirus 1, and calicivirus 2. On only 2 occasions was a virus of the same type (both adenoviruses) found by tissue culture as well as by electron microscopy.

In the stools of patients in group 4 no pathogens were found. Group 5 contained 3 patients who showed both rotavirus and pathogenic bacteria—*Salmonella berkeley*, *Salmonella typhimurium*, and *E. coli* O125.

Altogether 125 throat swabs were taken for virology and results of 17 (14%) were positive; they yielded adenovirus 4, enterovirus 2, cytomegalovirus 5, herpes simplex 1, respiratory syncytial virus 1, rhinovirus 3, and parainfluenza 1. 135 throat swabs were taken for bacteriology and results of 22 (16%) were positive; they comprised streptococci group A 3, streptococci group B 5, streptococci group C 1, *Streptococcus pneumoniae* 4, *S. faecalis* 1, and haemophilus species 8. In 5 patients a virus of the same group was isolated from both stool and throat (adenovirus 4, and enterovirus 1). The throat swabs and nasopharyngeal secretions examined by electron microscopy belonged to 9 patients with rotavirus and one with an adenovirus seen on stool electron microscopy. A papilloma virus was found in material from the throat swab of one patient who had rotavirus in the stool but no virus particles were identified in any other respiratory specimen.

The clinical features of the 4 main groups of stools were compared but the 3 patients in group 5 were excluded. The results for all 4 groups were tested for nonuniformity by the χ^2 test and reported as significant when $P<0\cdot05$. Clinical features were recorded before any microbiological results were received. Bacteriological reports were obtained within 3 days, but virology and electron microscopical examination were not completed until after the patient had been discharged from hospital and so could not bias the clinical observations.

At least one dose of an antibiotic was known to have been taken by 46 children before admission. These children included a few with bacterial infections, but the differences between the groups were not significant (35·5%, 17%, 27%, and 35% respectively, for groups 1 to 4).

Patients.

Sex

There were 88 (59%) boys and 62 (41%) girls. Sex ratios in the 4 stool groups were 58%, 65%, 58%, and 62% boys in groups 1 to 4 respectively, and these were not significantly different.

Age

Fig. 1 shows the ages of the patients. The youngest was 8 days old and the oldest 13 years. The 4 groups showed different patterns ($\chi^2 = 42\cdot9$, $P = 0\cdot008$). Rotavirus was most common in babies of between 6 and 18 months, and other viruses or no pathogens below 6 months, but bacterial pathogens occurred in fairly equal numbers at each age. 15 (10%) patients were less than 3 months of age and rotavirus was identified from only 2 of these babies.

Month of admission

Fig. 2 shows the seasonal pattern of admissions. Rotavirus infection occurred mainly in the first 6 months of the year with a peak in January and February. The other groups showed no pronounced seasonal pattern.

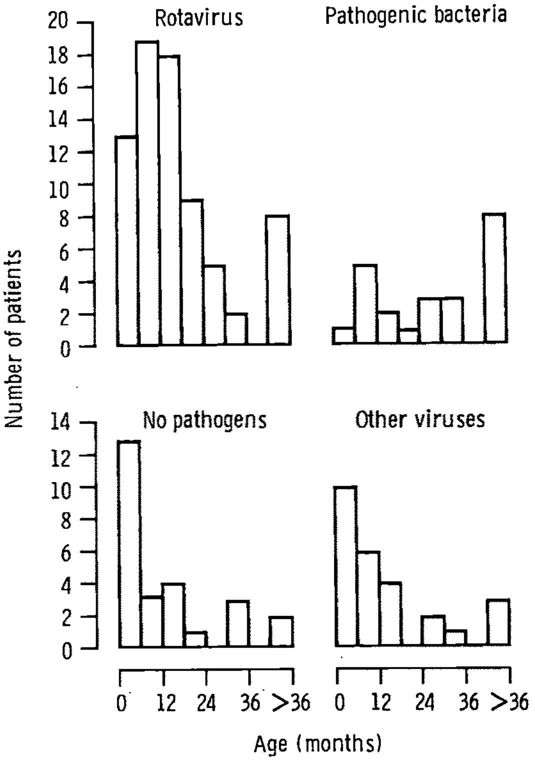

Fig. 1 *Age distribution of the patients.*

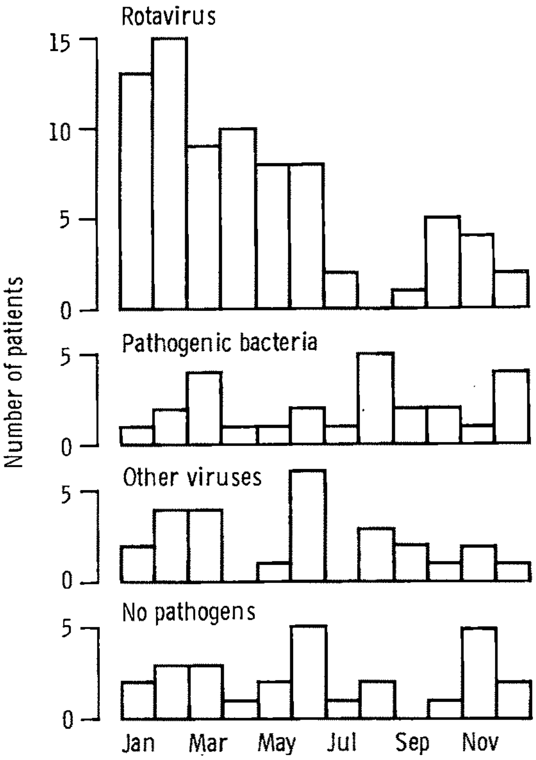

Fig. 2 *Monthly incidence of gastroenteritis.*

Clinical features.

Vomiting

69 (93%) out of 74 patients excreting rotavirus vomited for at least one day, compared with 10 (43%) out of 23, 14 (54%) out of 26, and 20 (77%) out of 26 in groups 2 to 4 respectively ($\chi^2 = 32{\cdot}6$, $P<0{\cdot}001$). Fig. 3 shows the number of patients who vomited for at least one, for at least 2, etc. days before and after admission, but not necessarily on consecutive days. In group 1 the median duration of vomiting was one to 2 days before admission, after which most patients either did not vomit at all or had stopped within 24 hours. A similar pattern was observed in the other groups. In groups 3 and 4 proportionately fewer patients vomited but they tended to vomit for longer ($\chi^2 = 42{\cdot}60$, $P = 0{\cdot}009$).

Diarrhoea

Patients were only included in the study if they had diarrhoea for at least one day, and Fig. 4 shows the number of days on which this was reported before and after admission. In the rotavirus group diarrhoea usually persisted for 2 to 3 days after admission, and the median total duration of diarrhoea was 4 to 5 days, with a mean of 5. In the other groups it lasted significantly longer, means of 7·3, 9·1, and 8·5 days in groups 2 to 4 respectively ($\chi^2 = 51{\cdot}5$, $P = 0{\cdot}003$). Blood in the stools was recorded only in the group with bacterial infection (10 (38%) out of 26) and in one patient in whom no pathogens were found.

Severity of dehydration

Intravenous fluids were administered to children with more than 5% dehydration clinically, and also to those who continued to vomit after they were given oral glucose electrolyte mixture. The use of IV fluids was taken as an index of the severity of dehydration. More rotavirus patients had IV fluids (39%), compared with 13%, 12%, and 23% in groups 2 to 4 respectively ($\chi^2 = 11$, $P = 0{\cdot}01$).

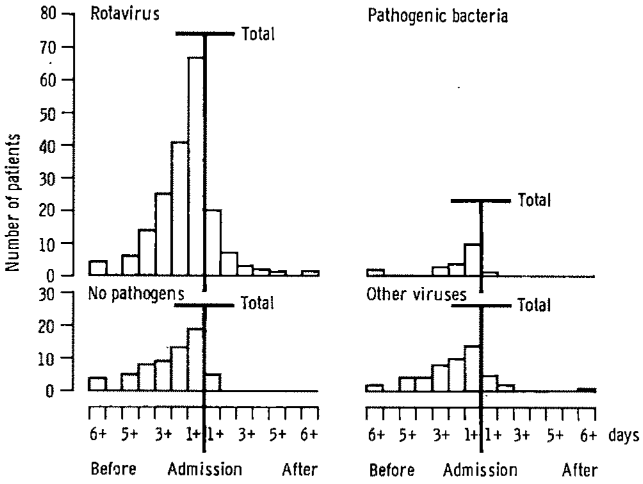

Fig. 3 *Number of days on which vomiting was recorded.*

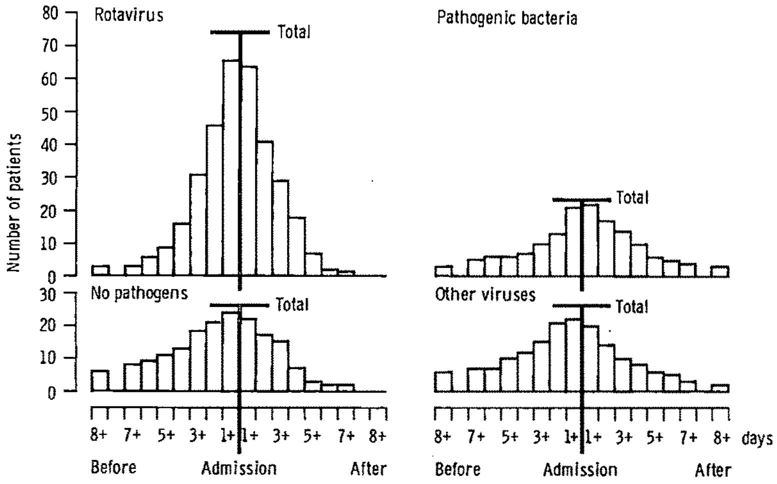

Fig. 4 *Number of days on which diarrhoea was recorded.*

Fig. 5 shows the proportion of patients of various ages that received IV fluids in the rotavirus group compared with the others. In the rotavirus group there was a highly significant peak at 12 to 18 months, when 75 % of patients excreting rotavirus were given IV fluids and 3 of them had hypernatraemic dehydration (plasma sodium >155 mmol/l).

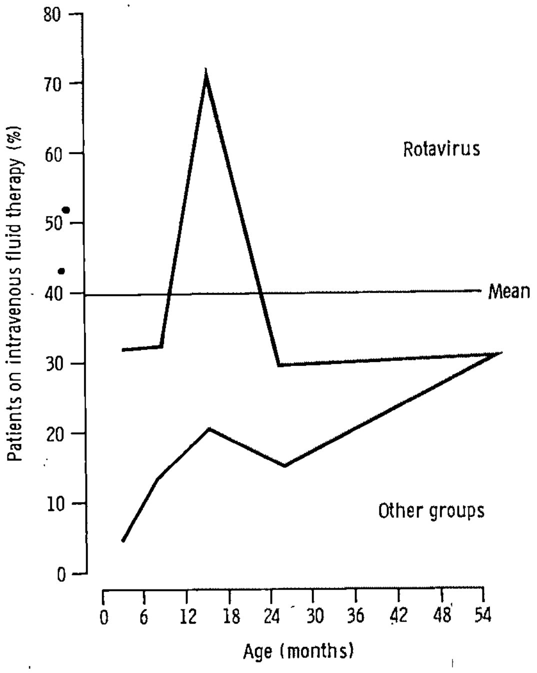

Fig. 5 *Relationship between age and treatment with intravenous fluids.*

Respiratory infection

Observations showing that the respiratory tract was affected are summarised in Table 2. A patient was classified as having respiratory involvement from all evidence of respiratory illness, either by the history or by clinical observations; on this basis 66 % of rotavirus patients had respiratory illness compared with 26 to 38 % of other groups ($\chi^2 = 16$, $P = 0{\cdot}01$).

There was no correlation between a positive bacterial or viral throat swab and respiratory illness ($\chi^2 = 0{\cdot}07$, $P = 0{\cdot}03$), nor with the patient being in the rotavirus or any other group ($\chi^2 = 4{\cdot}1$, $P = 0{\cdot}25$).

Incidence of fever

62 % of rotavirus patients had a maximum recorded rectal temperature of 37·5°C or more compared with 57 %, 58 %, and 58 % in the other groups, but the differences were not significant ($P = 0{\cdot}05$).

Discussion.

This study shows that diarrhoea attributed to rotavirus is more often associated with a respiratory illness than is diarrhoea attributed to other pathogens. A history of a preceding cough, nasal discharge, or otitis media was the outstanding clinical difference between rotavirus patients and the others. Likewise, after admission to hospital a red throat or red, bulging tympanic membranes were seen more often in the rotavirus patients than in others. Viruses and bacteria were isolated with equal frequency from the throat swabs of patients with respiratory symptoms as from those with no such symptoms. This suggests that the rotavirus, rather than any

Table 2 *Evidence of respiratory infection*

Clinical features	*Group 1* (*rotavirus*)	*Group 2* (*bacteria*)	*Group 3* (*other viruses*)	*Group 4* (*no pathogens*)	*Significance*
*History of cough, nasal discharge, or otitis before admission	40/74 (54)	3/23 (13)	7/26 (27)	7/26 (27)	$\chi^2 = 13\cdot4$ $P = 0\cdot04$
*Red throat observed in hospital	30/74 (41)	4/23 (17)	5/26 (19)	3/26 (12)	$\chi^2 = 11\cdot5$ $P = 0\cdot009$
Florid otitis media	20/74 (27)	3/23 (13)	2/26 (8)	3/26 (12)	$\chi^2 = 6\cdot78$ $P = 0\cdot08$
Nasal discharge	17/74 (23)	4/23 (17)	7/26 (27)	4/26 (15)	$\chi^2 = 1\cdot36$ $P = 0\cdot7$
Persistent cough	8/74 (11)	1/23 (4)	4/26 (15)	2/26 (8)	$\chi^2 = 1\cdot85$ $P = 0\cdot6$
Hoarse voice	3/74 (4)	0	2/26 (8)	0	$\chi^2 = 3\cdot32$ $P = 0\cdot34$
Lower respiratory tract infection	5/74 (7)	0	3/26 (12)	1/26 (4)	$\chi^2 = 3\cdot15$ $P = 0\cdot37$
*Any evidence of respiratory infection	49/74 (66)	6/23 (26)	8/26 (31)	10/26 (38)	$\chi^2 = 16\cdot1$ $P = 0\cdot01$

*Features occurring significantly more often in rotavirus patients ($P<0\cdot05$).
Percentages are shown in parentheses.

other agent, was responsible for the respiratory features.

However, no rotavirus particles were found by electron microscopical examination of nasopharyngeal secretions and throat swabs from 9 children with rotavirus in their stools and signs of an upper respiratory infection. The rotavirus may have been present in the upper respiratory tract at an earlier stage in the illness or in concentrations too low to be detected by electron microscopy (Davidson *et al.*, 1975).

Although this study showed a seasonal peak in winter (Fig. 2), rotavirus was isolated throughout the year. In temperate climates there may be endemic infection with superimposed winter epidemics; in tropical countries rotavirus is isolated particularly in the rainy season and is more common in areas of high humidity (T. H. Flewett, 1978, unpublished observation). Epidemics could be related to different serotypes (Fonteyne *et al.*, 1978; Zissis and Lambert, 1978) and transmitted by droplet infection via the respiratory tract, while endemic infection may be transmitted by the faeco-oral route.

Rotavirus illness was usually accompanied by vomiting which preceded the diarrhoea (Fig. 3). After admission to hospital, vomiting stopped but diarrhoea persisted for 2 or 3 days (Fig. 4). A few patients became rapidly dehydrated as a result of passing profuse watery stools even when they were receiving IV fluids only. The observation that diarrhoea attributed to rotavirus lasted for up to 5 days, despite admission to hospital, suggests that rational treatment can be planned from a clinical recognition of the syndrome. In the past, schemes for the management of dehydration associated with gastroenteritis have been constructed mainly for infants under one year of age infected with enteropathogenic *E. coli*. An electrolyte mixture is customarily given orally or intravenously for 24 hours; then the child is gradually weaned to full strength milk over 5 days. For the rotavirus syndrome it may be preferable to give an electrolyte mixture for 2 or 3 days, and then regrade rapidly if dilute milk or a light diet is tolerated. Our children were usually on a normal diet after 5 days and this regimen rarely produced prolonged diarrhoea.

The most severely dehydrated children excreting rotavirus were aged between 12 and 18 months, only 2% of the whole series had hypernatraemic dehydration and there was only one patient with persistent disaccharide intolerance. Recent surveys from Hackney (London) and Newcastle upon Tyne show a decline in the duration and severity of infantile gastroenteritis (*British Medical Journal*, 1977b; Pullan *et al.*, 1977; Tripp *et al.*, 1977) but severe dehydration and prolonged diarrhoea were still common in the very young babies. In the present study only 10% of the children were under 3 months, and from the younger babies, other viruses or no pathogens were found in the stools more often than rotavirus. A comparatively high incidence of early breast feeding in the area served by this hospital (Coles *et al.*, 1978) may account for the rarity of both recognised enteropathogenic serotypes of *E. coli* and early infection with rotavirus (Bullen, 1977; Thouless *et al.*, 1977). The practice of feeding low solute milks for the first months of life may have helped to prevent severe dehydration and hypernatraemia.

Comparison between this study and others in the UK should take into consideration the social and cultural background of the indigenous population. Neither social class nor ethnic group was recorded on the proforma, but in retrospect, 66 (44% of the total) patients were children of immigrants to this country who were predominantly Asian refugees from East Africa. Many lived in over-crowded accommodation and, in some cases, bacterial infection was imported from overseas either by the child himself or by another member of the household.

Rotavirus (group 1) and bacterial (group 2) patients should be compared with caution with groups 3 and 4 in which the nature of the pathogen is not established. No pathogens were found in 17% of children but there may have been unidentified viruses, or enteropathogenic strains of *E. coli* which were not detected by the serological methods used. Other studies show that complement-fixation tests on paired sera can detect rotavirus in patients whose stools were negative by electron microscopical examination (Kapikian *et al.*, 1975; Gomez-Barreto *et al.*, 1976; Gust *et al.*, 1977); as such examination is usually negative by 6 days after the onset of diarrhoea, rotavirus may have been missed in 8 cases with a longer history.

Except in the neonatal period, rotavirus is rarely identified in the stools of asymptomatic children (Albrey and Murphy, 1976; Totterdell *et al.*, 1976; Gust *et al.*, 1977; Murphy *et al.*, 1977) but the same is not true of other stool viruses (Stott *et al.*, 1967; Flewett *et al.*, 1974; Flewett, 1976; Madeley *et al.*, 1977). This study did not include a group with no diarrhoea but it was conducted concurrently with a study of viruses isolated from children of the same age who were admitted with febrile convulsions (Lewis *et al.*, 1979). There was no significant difference in the rate of isolation of enteroviruses or adenoviruses from the stools of these two groups of patients, but rotavirus was found in only 2 (3%) out of 62 children with febrile convulsions and each had a febrile illness followed by diarrhoea. Two children in the gastroenteritis study had febrile convulsions. One had an adenovirus isolated from the throat and stool and the other was infected with *Shigella sonnei*.

Despite the limitations of the comparative analysis, this survey has shown distinctive clinical features in patients excreting rotavirus; in particular, diarrhoea was not usually the first symptom. General practitioners and paediatricians should therefore consider rotavirus in the differential diagnosis of vomiting, unexplained dehydration, pharyngitis, acute otitis media, or an unexplained fever, particularly in children from 6 to 24 months of age and in winter.

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Plasma 17OH-progesterone concentrations in newborn infants

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SUMMARY Plasma concentrations of 17OH-progesterone were determined in 60 normal newborn infants aged between 3 and 36 hours. Mean levels decreased rapidly during this time after removal of the placental contribution of this steroid. A further 70 normal infants, studied between ages 2 and 7 days, showed a mean plasma 17OH-progesterone concentration of 3·5 nmol/l (1·2 ng/ml). By comparison, plasma concentrations in untreated infants with congenital adrenal hyperplasia were markedly raised. At 36 hours of age, there was an obvious difference between plasma levels of this steroid in normal and affected infants. Determination of plasma 17OH-progesterone concentrations are valuable in the evaluation of disorders of sexual differentiation and electrolyte balance in newborn infants, provided due care is given to the timing of sample collections.

It is now well established that plasma concentrations of 17OH-progesterone are markedly raised in untreated congenital adrenal hyperplasia (CAH) due to C-21 hydroxylase enzyme deficiency (Barnes and Atherden, 1972; Youssefnejadian and David, 1975; Hughes and Winter, 1976). Consequently, requests for measuring this steroid in plasma collected from newborn infants with ambiguous genitalia are increasing in frequency. The Supraregional Assay Service Laboratory at the Tenovus Institute receives numerous blood samples each week for determination of plasma 17OH-progesterone concentrations. Many of these samples have been collected within the first 48 hours of life at a time when, because of placental 17OH-progesterone production (Tulchinsky and Simmer, 1972), plasma concentrations are raised in normal newborn infants. There is a limited amount of information on plasma concentrations of 17OH-progesterone during early life and on the time taken for levels to decrease to values observed in later infancy and childhood. This report gives data on plasma 17OH-progesterone concentrations in mixed cord blood and in a group of normal newborn infants studied during early postnatal life. The results are compared with those found in untreated newborn infants with CAH.

Patients and methods

Mixed cord blood samples were obtained from 19 babies (10 boys and 9 girls) immediately after cord clamping. Their gestational ages ranged from 37 to 41 weeks. Capillary blood was collected by heel prick from 60 infants who were products of uneventful term pregnancies. There were 32 boys and 28 girls, whose postnatal ages ranged from 3 to 36 hours at the time of sample collection. Maternal consent for the study was obtained in each case. Plasma samples collected from 70 infants up to 7 days' postnatal age and sent to this laboratory were also available for analysis. Several infants with CAH due to C-21 hydroxylase deficiency were studied during the first week of life before starting steroid replacement therapy. Their plasma 17OH-progesterone concentrations were compared with those determined in normal infants.

Plasma 17OH-progesterone was measured by radioimmunoassay (RIA) using an antiserum kindly donated by Dr D. L. Loriaux, NIH, Bethesda. The sensitivity of the assay was 4 pg/tube using 200 μl plasma. Apart from 11-deoxycortisol (3·3%) and 21-deoxycortisol (1·6%), the cross-reactivity of the 17OH-progesterone antiserum with numerous other steroids, including progesterone, was less than 0·1% The intra-assay coefficient of variation was ± 6·3%; the inter-assay coefficient of variation was ± 7·5% (high pool) and 11·9% (low pool). All RIA data processing was performed using the method of

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Rodbard and Hutt (1974) and quality controlled by the method of Kemp *et al.* (1978). The mathematical relationship between plasma concentration (Y) and the age of the newborn infant (t) was reasonably described by a power function of the form $Y = At^B$ within the time-span of sampling. The index of determination was 0·72 and values of A and B determined by least squares analysis of data contained in Fig. 1, using a linear transformation of this equation, were 151 and −0·906 respectively.

Results

Mean values for plasma 17OH-progesterone concentrations in mixed cord blood were 203 ± 37·8 SD nmol/l (69 ± 12·9 ng/ml) for boys and 184 ± 34·5 SD nmol/l (62·6 ± 11·7 ng/ml) for girls. There was no significant sex difference. The individual plasma 17OH-progesterone concentrations for 60 newborn infants in relation to postnatal age are shown in Fig. 1. The line represents the mean plasma 17OH-progesterone concentration for the whole group of infants, there being no significant difference between mean concentrations in boys and girls. The mean plasma 17OH-progesterone concentration fell rapidly after birth, from 45 nmol/l (16 ng/ml) at 12 hours, to 8·5 nmol/l (2·9 ng/ml) at 24 hours, and 6 nmol/l (2 ng/ml) by 36 hours of age. This represents a 32-fold decrease from the mean cord plasma 17OH-progesterone concentration. The pattern of plasma 17OH-progesterone concentrations in normal infants during the first week of life is shown in Fig. 2. Mean levels reached a nadir of about 3·5 nmol/l (1·2 ng/ml) by 7 days of age. This contrasts with plasma 17OH-progesterone concentrations in untreated CAH infants during the first 7 days of life. At 12 hours' postnatal age, there was a wide difference between plasma 17OH-progesterone concentrations in normal and CAH infants. By the 2nd day there was a 40-fold

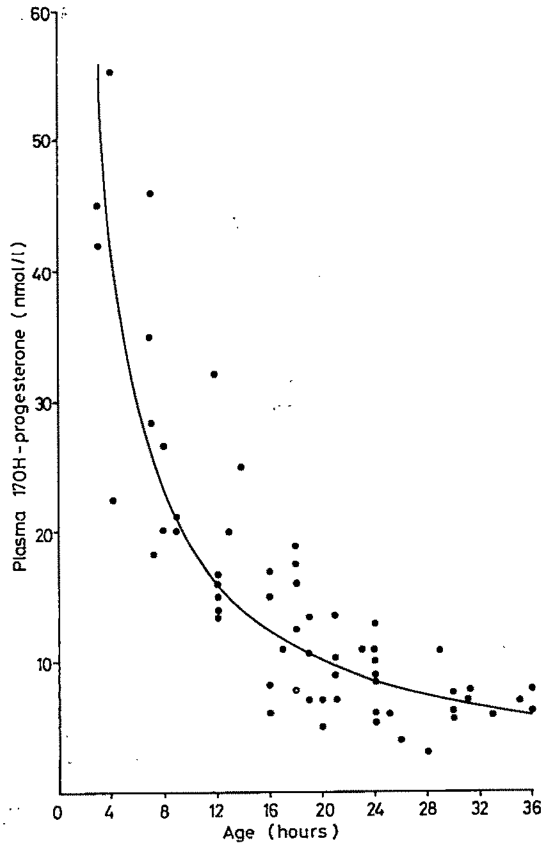

Fig. 1 *Plasma 17OH-progesterone concentrations in normal infants during the first 36 hours of life. The line represents the mean plasma concentration of this steroid in baby boys and girls.*

Conversion: SI to traditional units—17OH-progesterone: 1 nmol/l ≈ 0·31 ng/ml.

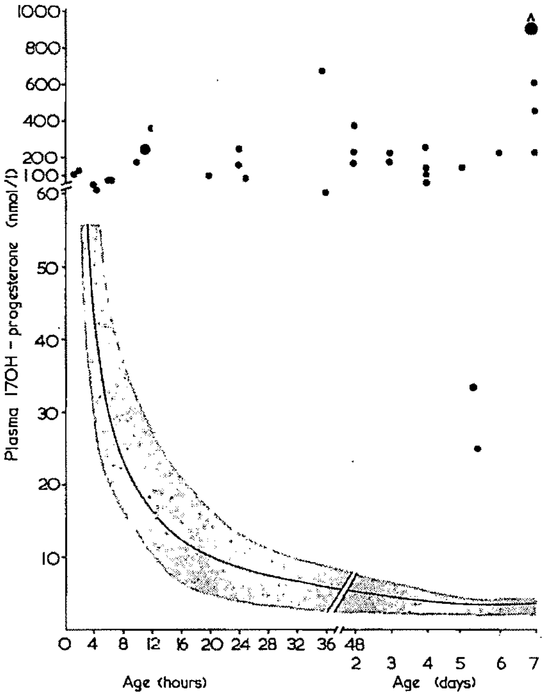

Fig. 2 *Plasma 17OH-progesterone concentrations in normal and CAH infants during the first 7 days of life. The line represents the mean and the shaded area encompasses the range of plasma concentrations in normal babies. Also shown are individual plasma 17OH-progesterone concentrations determined in untreated CAH infants.* ▲ *represents a value of 2430 nmol/l (826 ng/ml).*

difference in mean plasma 17OH-progesterone concentrations.

Discussion

This study confirms previous reports of a raised cord plasma 17OH-progesterone concentration reflecting placental production of this steroid (Jenner *et al.*, 1970; Lippe *et al.*, 1974; Winter *et al.*, 1976). There are two recent studies which give data on plasma 17OH-progesterone concentrations during the first 24 hours of life of newborn infants (Forest and Cathiard, 1978; Sippell *et al.*, 1978). Both report the rapid fall in plasma levels within hours of birth, reaching a nadir by about 5 to 7 days of age. The results now reported confirm and extend this observation in a larger group of infants also studied during the first week of life. As measurement of plasma 17OH-progesterone is so valuable in the early diagnosis of CAH, a comparison was made between results of plasma 17OH-progesterone determinations in normal and CAH infants. The data clearly show that, by 36 hours' postnatal age, there is a pronounced difference between the two groups.

Congenital adrenal hyperplasia is the most common cause of ambiguous genitalia of the newborn (Hughes, 1977). In many instances, plasma 17OH-progesterone measurements will also aid in the assessment of other conditions. In addition, some infants who are stressed—for example, due to infection—have concentrations of plasma 17OH-progesterone up to 30 nmol/l (10 ng/ml) at 5 to 7 days of age. However, plasma 17OH-progesterone concentrations exceed 200 nmol/l (68 ng/ml) in untreated CAH infants of this age.

Therefore, determination of plasma 17OH-progesterone concentrations in the neonatal period can be extremely useful for the differential diagnosis of ambiguous genitalia, electrolyte disturbances, or for the investigation of baby boys with a positive family history for CAH (Hughes and Winter, 1977). It is recommended that plasma samples should be collected after 24 hours' postnatal age in order to eliminate the placental influence on plasma 17OH-progesterone levels. The exact age of the infants, in hours, at the time samples are collected should be known.

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Continuing need for mineralocorticoid therapy in salt-losing congenital adrenal hyperplasia

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SUMMARY Four patients with salt-losing congenital adrenal hyperplasia (CAH) who had stopped mineralocorticoid therapy for several years, showed raised plasma concentrations of 17OH-progesterone and plasma renin activity, despite adequate glucocorticoid therapy. One patient was able to reduce urinary sodium excretion when the sodium intake was restricted. Another patient who was a salt-loser, developed signs of an adrenal crisis when salt deprived. In comparison, one nonsalt-loser and 2 normal subjects decreased urinary sodium excretion in response to sodium restriction. The addition of fludrocortisone (100 μg) to usual maintenance doses of glucocorticoid, resulted in normal levels of plasma 17OH-progesterone and plasma renin activity in all 4 salt-losers. Two female salt-losers, with raised plasma testosterone concentrations, began menstruating when their plasma testosterone concentrations returned to normal after treatment with fludrocortisone. It is recommended that salt-losing CAH patients should be given mineralocorticoid, in addition to glucocorticoid therapy, at least until adult life.

About one-third to one-half of patients with congenital adrenal hyperplasia (CAH) due to C21-hydroxylase enzyme deficiency are salt-losers. This loss occurs within the first 2 weeks of life and patients require immediate mineralocorticoid replacement. However, they appear to require less salt later and it has been suggested that mineralocorticoid therapy can be discontinued at age 4 years (Newns, 1974). There is evidence that this regimen will lead to inadequate control in these patients. A pronounced increase in plasma concentrations of 17OH-progesterone and plasma renin activity occurs in some salt-losers, in spite of apparently adequate glucocorticoid replacement (Hughes and Winter, 1976; Grant *et al.*, 1977). The consequences of persistent raised levels of plasma steroid precursors are unknown. A group of salt-losing CAH patients, in whom mineralocorticoid treatment had been discontinued for several years, was studied to evaluate the metabolic responses to a restricted sodium diet and the reintroduction of mineralocorticoid therapy.

Patients and methods

Six patients with CAH due to C21-hydroxylase deficiency were initially included in the study. One boy, however, developed a salt-losing crisis as a result of gastroenteritis. Mineralocorticoid treatment was restarted and he was excluded from the study. Clinical details of the remaining patients are shown in Table 1. The salt-losers had hyponatraemic dehydration and hyperkalaemia soon after birth. They were treated with hydrocortisone (or cortisone acetate), fludrocortisone, and supplemental salt in the milk feeds. For comparison, a 13-year-old girl with nonsalt-losing CAH and two female student dietitians without evidence of endocrine disease were also studied.

Dietary histories were recorded for each patient, with particular reference to sodium intake. Patients were maintained on their usual doses of glucocorticoid during the study. Venous blood was collected between 0900 and 1000 hours for determination of plasma concentrations of 17OH-progesterone, testosterone, and plasma renin activity. 24-hour urine collections were performed for measurement of sodium and potassium excretion. Patients and controls were then placed on a dietary intake of 20 mmol sodium/day (potassium 75 mmol/day) for 4 days under supervision in hospital. Plasma and urinary studies were repeated at the end of this

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Table 1 *Clinical details of subjects studied*

Case	*Sex (M/F)*	*SL/NSL*	*Age at study (years)*	*(Age fludrocortisone discontinued (years)*	*Years without fludrocortisone*
1	F	SL	9	4	5
2	F	SL	13	10	3·5
3	F	SL	14	8	6
4	M	SL	14	7	7
5	F	NSL	13	—	—
Control	F	—	19	—	—
Control	F	—	20	—	—

SL = salt-loser; NSL = nonsalt-loser.

period, when venous blood was collected from subjects in the standing position. Salt-losers were then treated with fludrocortisone 100 μg daily in addition to their usual glucucorticoid therapy. Measurement of plasma concentrations of 17OH-progesterone, testosterone, and plasma renin activity was repeated after 3 months.

Plasma 17OH-progesterone was determined by radioimmunoassay using an antiserum supplied by Dr D. L. Loriaux, NIH, USA. The sensitivity of the assay was 4 pg/tube. The intra-assay and interassay coefficients of variation were less than 6·3 and 11·9% respectively. Apart from 11-deoxycortisol (1·8%) and 21-deoxycortisol (1·6%), the cross-reactivity of the antiserum with numerous other corticosteroids, including progesterone, was less than 0·1%. Plasma testosterone was measured by radioimmunoassay as previously described (Hillier *et al.*, 1973). Plasma renin activity was measured by radioimmunoassay of the angiotensin I generated after standard incubation of plasma (Haber *et al.*, 1969). The mean level of plasma renin activity in healthy ambulant adults was 1·17±0·5 SEM ng/ml per hour.

Results

When studied, all salt-losers were taking more than 200 mmol sodium per day in their diet apart from table salt added to food. The results of baseline studies performed while on this sodium intake are shown in Table 2. The mean plasma 17OH-progesterone concentration in salt-losers was markedly raised, despite a hydrocortisone dose in the range of 20–32 mg/m^2 per day (mean dose 25 mg/m^2 per day). Two female salt-losers showed raised plasma testosterone concentrations and plasma renin activity was increased in all salt-losers. In comparison, the nonsalt-loser had normal plasma 17OH-progesterone and testosterone concentrations and a slightly raised plasma renin activity. All values were normal in the control subjects. The effects of sodium restriction in the control subjects and the nonsalt-loser (Case 5) are shown in Fig. 1. All showed a slight increase in plasma 17OH-progesterone concentrations and a rise in plasma renin activity, which was more pronounced in the nonsalt-loser. Urinary sodium excretion decreased to approximately 20 mmol/day in all 3 subjects in response to sodium restriction. Results obtained in one salt-loser (Case 1) are shown in Fig. 2. This patient was also able to reduce urinary sodium excretion, but the increases in plasma renin activity and plasma 17OH-progesterone were more pronounced. Fig. 3 shows the results obtained in two other salt-losers (Cases 2 and 4). Plasma 17OH-progesterone concentrations in both patients were markedly raised before the dietary period and increased further after sodium restriction. Neither patient was able to suppress urinary sodium excretion in response to a low sodium intake, nor was there an apparent change in levels of plasma renin activity. Unfortunately, neither patient in this instance was sampled for plasma renin activity in the standing position (Haber *et al.*, 1969). The 4th salt-loser (Case 3) did not tolerate the diet (Fig. 4). Plasma 17OH-progesterone

Table 2 *Plasma steroid and renin concentrations before salt restriction*

Subjects	*17OHP (nmol/l)*	*Testosterone (nmol/l)*	*Plasma renin activity (ng/ml per hour)*	*Hydrocortisone dose (mg/m^2 per day)*
Salt-losers	364	3·1	3·3	25
Nonsalt-loser	3·6	0·4	2·2	21
Controls	4·5	—	0·74	—

17OHP = 17OH-progesterone.
Mean values are shown (testosterone results in women only).
Conversion: SI to traditional units—17OHP: 1 nmol/l ≈ 0·31 ng/ml; testosterone: 1 nmol/l ≈ 0·29 ng/ml.
Traditional to SI units—angiotensin I: 1 ng/ml per hour ≈ 0·77 pmol/ml per hour.

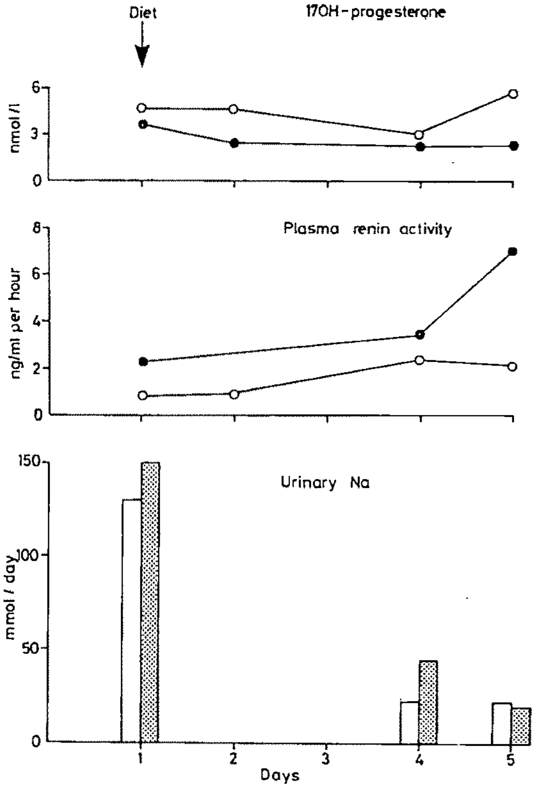

Fig. 1 *Effect of sodium restriction on plasma 17OHP, plasma renin activity, and 24-hour urinary Na secretion in controls* (○□) *and a nonsalt-loser, Case 5* (●▨).

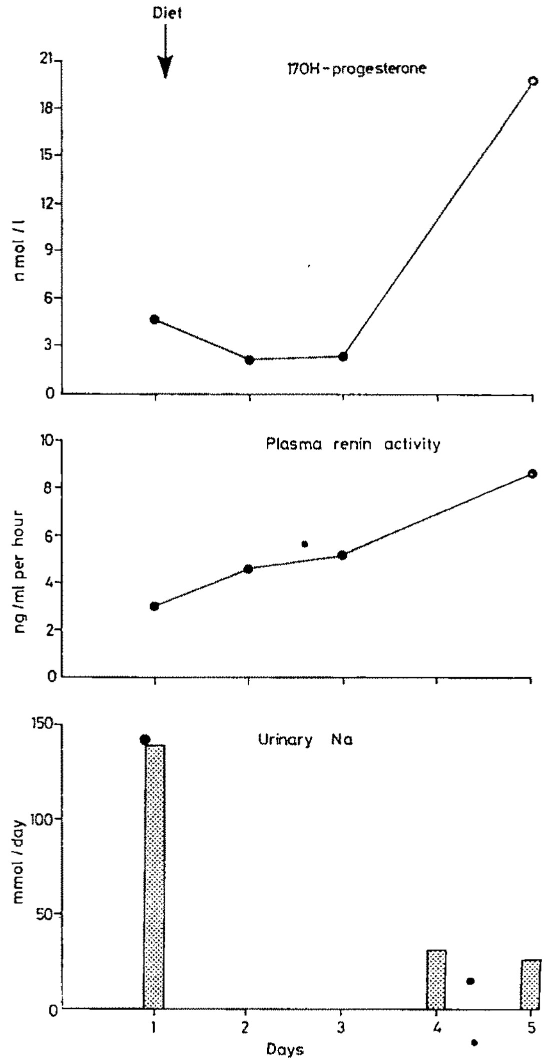

Fig. 2 *Response to sodium restriction in Case 1, a salt-loser.*

concentrations increased further from the previous high values and plasma renin activity increased to 60 ng/ml per hour. There was a 3 kg loss in body weight and the patient showed signs of an adrenal crisis after only 2 days' salt restriction. The study was discontinued and IV saline was given. This treatment, together with subsequent fludrocortisone therapy, resulted in plasma 17OH-progesterone concentrations and plasma renin activity returning towards normal levels and a regain to normal body weight. Urinary sodium excretion was not measured in this patient.

The results of hormone measurements performed after 3 months of treatment with 100 μg fludrocortisone are shown in Table 3. For comparison, the results of baseline studies (Table 2) are also given. The dose of glucocorticoid had remained constant

Table 3 *Plasma steroid and renin concentrations before and after fludrocortisone therapy*

Subjects	*17OHP (nmol/l)*		*Testosterone (nmol/l)*		*Plasma renin activity (ng/ml per hour)*		*Hydrocortisone dose (mg/m² per day)*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
Salt-losers	364	27	3·1	1·0	3·3	1·03	25	25
Nonsalt-loser	3·6	1·0	0·4	0·6	2·2	0·57	21	21

Mean values are shown. See Table 2 for conversion factors.

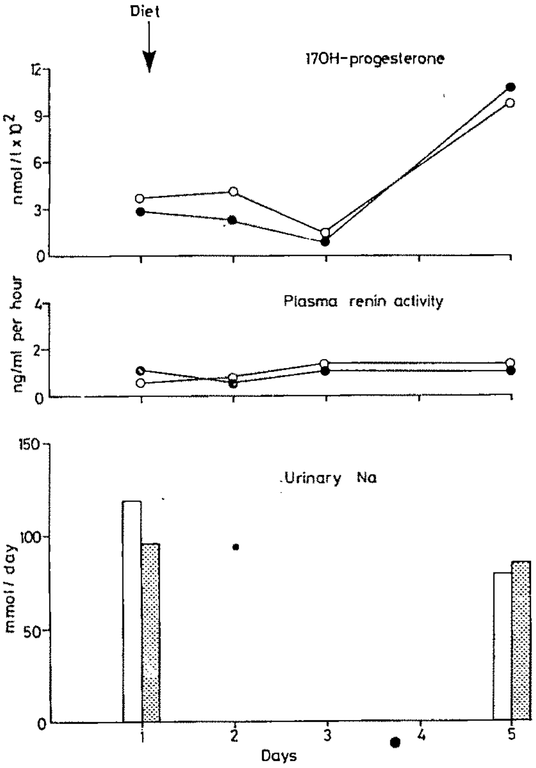

Fig. 3. *Effect of sodium restriction in 2 salt-losers, Case 2 (□), and Case 4 (▨). The units on the 17OHP ordinate are increased by 10^2.*

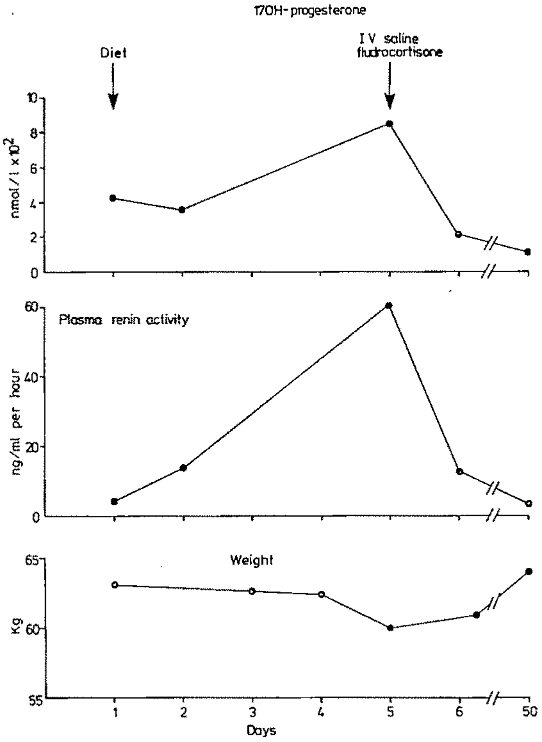

Fig. 4 *Effect of sodium restriction in salt-loser, Case 3. Urinary Na values are not shown in this figure. The units on the 17OHP ordinate are increased by 10^2.*

during this time. The mean plasma 17OH-progesterone concentration was now less than 30 nmol/l (9·4 ng/ml), considered normal for adequately treated CAH patients (Chaussain *et al.*, 1974; Hughes, 1977). Plasma testosterone concentrations and levels of plasma renin activity were also normal. During this time, 2 female salt-losers had started menstruating.

Discussion

This study confirms the suggestion that older children with salt-losing CAH can tolerate a reduction or even a cessation in mineralocorticoid treatment. However, this is compensated for by a high salt intake. The excessive sodium intake may be harmful over a long period. In their study of 3 children with hypoaldosteronism, Hamilton *et al.* (1976) suggested that in the face of sodium depletion, continuing a high sodium intake may have the effect of producing a high filtered water load in the kidney. This may in turn reduce renin production and hence the stimulus for aldosterone secretion. In such a situation, it is more rational to increase sodium reabsorption using a salt-retaining hormone. A high salt intake in childhood may be associated with the subsequent development of hypertension in adult life (Rose, 1977).

In this study, persistent salt depletion was suggested by increased levels of plasma renin activity in all but one of the salt-losers, despite normal serum electrolytes. This agrees with previous observations that measurement of plasma renin activity is an extremely sensitive index of sodium balance in salt-wasting disorders such as CAH (Dillon and Ryness, 1975; Hughes and Winter, 1977). All the salt-losers showed markedly raised plasma concentrations of 17OH-progesterone, indicating poor control, although they were receiving a hydrocortisone dose (25 mg/m² per day) considered appropriate for maintenance therapy (Brook *et al.*, 1974; Hughes and Winter, 1976). Limal *et al.* (1977) have also recently demonstrated raised concentrations of plasma renin activity, 17OH-progesterone, and aldosterone in a group of salt-losers treated only with hydrocortisone.

Two female salt-losers in our study had increased plasma concentrations of testosterone. This was not surprising in view of the significant correlation between plasma concentrations of 17OH-progesterone and testosterone in prepubertal and adolescent female CAH patients (Hughes and Winter, 1978). Persistently raised plasma testosterone concentrations in adolescent girls may result in menstrual disorders and possibly in reduced fertility (Kirkland *et al.*, 1974). It may not have been mere coincidence, therefore, that these two female salt-losers started menstruating after fludrocortisone therapy and a return to normal plasma testosterone concentrations.

Salt restriction exaggerated mineralocorticoid deficiency in these salt-losers. The nonsalt-loser (Case 5) and one salt-loser (Case 1) were both able to reduce urinary sodium excretion in response to a low sodium diet, although compared with the controls, they both showed a greater rise in plasma renin activity. Two other salt-losers in our study (Cases 2 and 4) failed to suppress urinary sodium excretion while on the diet. Their high plasma 17OH-progesterone concentrations increased still further, but no rise in plasma renin activity was demonstrated owing to an error in sampling technique. Salt restriction precipitated an adrenal crisis in one patient (Case 3) who required parenteral saline therapy. This patient and the boy excluded from the study because of an episode of gastroenteritis are examples of a severer degree of salt-wasting. The results suggest a variable degree of salt deficiency even within the small group of salt-losers examined in this study. Some patients are at serious risk of developing a life-threatening adrenal crisis if their salt intake is restricted.

What factors contribute to poor control in these salt-losing patients? There is evidence that infusion of angiotensin II (a polypeptide stimulated by increased plasma renin activity) can directly stimulate ACTH release in normal subjects (Rayyis and Horton, 1971). A recent study of sodium balance in CAH showed a significant correlation between plasma concentrations of ACTH and plasma renin activity (Rösler *et al.*, 1977). The degree of ACTH stimulation was proportional to the amount of sodium loss. Salt depletion may itself result in chronic 'stress' and an enhanced ACTH production. The effect of increased ACTH production from whatever cause is an increased secretion of adrenal steroid precursors in CAH—such as progesterone, 17OH-progesterone, and 16OH-progesterone. These corticosteroids, when secreted in excess, have natriuretic activity in humans (Janoski, 1977). Their sodium-losing effect is probably through a competitive inhibition of aldosterone in the renal tubule, which explains the increased aldosterone production rates documented in nonsalt-losing CAH patients (Bartter *et al.*, 1968).

In our patients, adding fludrocortisone to their treatments resulted in normal plasma concentrations of 17OH-progesterone, testosterone, and plasma renin activity. The dose of fludrocortisone (100 μg) would not have provided sufficient glucocorticoid effect to account for this improvement. It must be concluded, therefore, that as glucocorticoid therapy remained unchanged throughout this study, these salt-losers were chronically salt depleted and improved after mineralocorticoid therapy. Grant *et al.* (1977) added fludrocortisone to the treatment of a larger group of salt-losers. Not all their patients responded with a decrease in plasma steroid and plasma renin concentrations. However, only 50 μg fludrocortisone was used and the patients were studied again after one month of treatment. Our results show conclusively that salt-losing CAH patients continue to require salt-retaining hormones throughout childhood and early adult life. Achieving normal sodium balance in such patients may well allow a reduction in glucocorticoid therapy and thereby an improvement in growth potential.

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Effects of pethidine and its antagonists on the newborn

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SUMMARY Nalorphine and naloxone were compared as to their effectiveness as pethidine antagonists. 85 infants were divided into a control group comprising 19 newborn babies whose mothers did not receive pethidine and the babies received no antagonist, and three groups in which the mothers all received pethidine and the babies had either no antagonist (24), nalorphine IV (16), or naloxone IV (26). All the babies were assessed by measuring their neurobehavioural states and respiratory functions. A further 12 newborn babies had naloxone plasma levels measured by radioimmunoassay. Although standard doses of nalorphine effectively antagonised the depressive effect on respiration induced by pethidine, there was a pronounced and undesirable excitatory agonist action. Naloxone was not observed to have any agonist activity, but the recommended IV dose (0·01 mg/kg) had only a slight and delayed antagonist action as measured by respiratory function tests. A more rapid and improved antagonism was noted after this dose was doubled (0·02 mg/kg). The plasma elimination-phase half-life of naloxone after intravenous cord injection was about 3 hours.

The narcotic antagonist naloxone became available in the UK in 1976, but there are few reports of its use in newborn babies. Naloxone can restore respiratory function to normal after depression induced by pethidine (Evans *et al.*, 1976; Gerhardt *et al.*, 1977; Wiener *et al.*, 1977). Studies in animals and man have shown that the main advantage of naloxone over nalorphine is its freedom from agonist activity, while a disadvantage is that its effect after IV injection seems to be of short duration. However, Wiener *et al.* (1977) showed this effect could be prolonged to 24–48 hours or longer by a single, large IM injection. These workers also demonstrated the ability of naloxone to restore neurobehavioural function in the newborn babies of mothers who had received pethidine.

Nalorphine was the standard narcotic antagonist used in the newborn until the introduction of naloxone, but their antogonist activities have not been compared. This study was therefore designed to compare the action of these two drugs, to assess the effect of currently recommended doses of naloxone, and to determine its plasma levels and half-life in the newborn baby.

Methods

Informed written consent for the study was obtained from the parents before labour was established. Only babies born at term (37–42 weeks) after a normal pregnancy, labour, and delivery were studied; babies with a cord blood pH of $<7·25$, babies who did not respond to simple resuscitative measures, and babies with any significant abnormalities were excluded. 85 newborn babies were divided at random into four groups. In the control group (group 1, $n = 19$) the mothers had received no pethidine during labour and their babies received no antagonist. A few mothers received epidural analgesia and/or Entonox, but no other analgesic or sedative was used. In the other groups the mothers had received IM pethidine within 4 hours of delivery but no other analgesic or sedative, apart from Entonox. Treatment of the newborn was randomised so that group 2 ($n = 24$) received no narcotic antagonist, and group 3 ($n = 16$) received nalophine and group 4 ($n = 26$) naloxone between one and 2 minutes after delivery. The antagonist was injected directly into the cord vein as close to the umbilicus as

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possible and 'milked' inwards before the cord was reclamped at the site of injection. Apart from 3 newborn babies who received 0·7 mg nalorphine at the start of the study, the dose of this drug was standardised at 0·5 mg. Group 4 were divided into two different dose regimens: the recommended IV dose (0·01 mg/kg$\simeq$0·035 mg) was given to 14 babies in group 4A and, after evaluating the results of this treatment, 12 babies (group 4B) were given double this dose (0·07 mg).

The newborn babies were assessed clinically in three ways. The wakefulness of each was recorded at 15, 30, and 90 minutes and again between 12 and 24 hours, using the six states described by Brazelton (1973). At 90 minutes and again between 12 and 24 hours the sucking reflex was assessed, using the method of Scanlon *et al.* (1974), and between 12 and 24 hours of age a Scanlon neurobehavioural score was performed by two paediatric registrars who were unaware of the treatment the mother and baby had received.

As part of the respiratory function assessment, the times from delivery to the 1st breath and to sustained respiration were noted, together with the routine recording of Apgar scores. During the definitive tests of respiratory function the babies were nursed in a heated cot in which the skin temperatures were maintained within the neutral thermal range (36·0–36·5°C) by servo-control. If possible the measurements were performed with the newborn in a stable state, although this was difficult in group 3. The main test of respiratory function was the measurement of carbon dioxide (CO$_2$) output, from which, together with heel prick arterialised capillary blood pCO$_2$, alveolar ventilation was calculated (alveolar ventilation = expired CO$_2$ × barometric pressure/pCO$_2$, corrected for temperature and humidity). These estimations and full blood–gas analyses were done at 15, 30, and 90 minutes and finally between 12 and 24 hours after delivery. Carbon dioxide output was determined using a technique derived from open-circuit methods previously described (Kappagoda *et al.*, 1974; Newell *et al.*, 1976; Evans *et al.*, 1977). Expired CO$_2$ was measured using an infrared gas analyser*, and the overall error of the calculated expired carbon dioxide output with this system was less than ± 5% (Thompson *et al.*, 1979). Statistical evaluation was done with Student's *t* test.

Heel prick blood samples were collected from a separate group of 12 newborn babies for determination of plasma naloxone levels by radioimmunoassay. It was necessary to use different babies because sampling disturbed the baby sufficiently to invalidate the respiratory function result as representing the 'basal' state. Half of them had received 0·035 mg and half 0·07 mg naloxone injected into the umbilical vein. The assay was such that 2 ng naloxone displaced the radiolabelled tracer, ^{3}H-naloxone, by 50%. The presence of pethidine in concentrations of up to 400 ng per sample caused no displacement. Each assay was carried out in duplicate with 0·2 ml heparinised plasma. Although the main metabolites of naloxone were not available to test for crossreactivity, current evidence suggests that they would be unlikely to interfere with the assay in the concentrations likely to be found in plasma (Berkowitz *et al.*, 1975).

Results

The items of clinical relevance are shown in Table 1. The mean maternal pethidine doses and the mean pethidine-to-delivery time intervals of the three groups of mothers receiving pethidine were not significantly different. Despite randomisation the difference between the mean birthweights of the no antagonist babies and those in group 3 was significant ($P<0·05$), but when compared with the mean birthweights of the other groups this was probably not of clinical importance. That the newborn had not been subject to intrauterine hypoxia is suggested by the normal cord blood pH findings, the slight differences

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*Analytical Development Co. Ltd. type 901; P. K. Morgan Ltd.

Table 1 *Mean (± SD) of maternal pethidine dose, pethidine-delivery interval, birthweight, cord blood pH, Apgar score, and time to sustained respiration*

Group	*Maternal pethidine dose (mg)*	*Pethidine/delivery interval (min)*	*Birthweight (g)*	*Cord blood pH*	*Apgar (1 min)*	*Time to sustained respiration (seconds)*
Controls (Group 1, n = 19)	—	—	3588 (487)	7·37 (0·05)	8·3 (0·05) P<0·002	30 (16) P<0·01
Maternal pethidine						
No antagonist (group 2, n = 24)	115 (28)	107 (56)	3683 (505) P<0·05	7·36 (0·05)	7·6 (0·9)	55 (34)
Nalorphine (group 3, n = 16)	106 (17)	108 (56)	3388 (382)	7·34 (0·05)	7·8 (0·9) P<0·01	52 (41) P<0·01
Naloxone (group 4, n = 26)	112 (33)	93 (49)	3469 (446)	7·35 (0·04)	7·8 (0·7)	56 (30)

between the groups being of no significance. There was, however, evidence of pethidine intoxication as reflected in the Apgar score, the mean one-minute value of 7·6 for the no-antagonist group being lower than the 8·3 for the control group ($P<0{\cdot}002$). Likewise, failure to establish respiration normally was seen in the 3 pethidine-treated groups in that the time to sustained respiration was prolonged (52–56 seconds) when compared with the control group (30 seconds, $P<0{\cdot}01$). Groups 3 and 4 showed a similar initial degree of respiratory depression, but because of the smaller numbers the differences were not all of statistical significance.

The Brazelton state score indicated that the newborn babies in all groups were in a rather wakeful condition for the first 90 minutes (range of mean scores 3/6 to 5/6) but that they had settled by the 12–24-hour assessment (range 1·7/6–1·9/6). Infants in group 3 tended to be fretful and irritable with high pitched cries, and their scores were appropriately high (range 5/6–6/6 at 15 and 30 minutes). This was associated with a poor mean Scanlon sucking score at 90 minutes of 1·0/3 compared with > 1·9/3 for the other groups. By 12–24 hours there was a difference in the sucking scores between the controls (1·3/3) and group 3 (1·8/3), but there was no obvious difference between the no-antagonist and the antagonist-treated groups. There was no significant difference in the mean and decrement values for the Scanlan and neurobehavioural scores (group 1, 18·00 ± 6·18 and 18·33 ± 6·93; group 2, 19·23 ± 3·98 and 15·31 ± 6·29; group 3, 18·57 ± 4·22 and 14·47 ± 8·61; group 4A and B, 18·07 ± 4·46 and 17·5 ± 5·26).

Multiple statistical comparisons were made between the mean pH, pO$_2$, pCO$_2$, and base deficit measurements from each group. Many of the differences were statistically significant (e.g. pH at 15 and 90 minutes between group 1 and 2, $P<0{\cdot}001$; pH at 15 minutes between group 1 and group 4A, $P<0{\cdot}05$, and group 4B, $P<0{\cdot}001$). The results show that there was respiratory depression in group 2 and even in group 4A. Babies in group 4B fared rather better, and these trends are in keeping with the results of the specific respiratory function studies that follow.

Tables 2 and 3 show the values for total expired carbon dioxide (CO$_2$ output) and alveolar ventilation in the four groups. At all times group 2 showed a consistent reduction in both these parameters compared with group 1 ($P<0{\cdot}01$ for CO$_2$ output at 15 and 30 minutes and alveolar ventilation at 15 minutes). By 12–24 hours the difference in CO$_2$ output was less significant ($P<0{\cdot}02$) and the differences in alveolar ventilation were no longer significant.

In group 3 the values for CO$_2$ output and alveolar ventilation were consistently higher at 15, 30, and 90 minutes than those of group 1. They were also significantly higher than those of group 2 at 15, 30,

Table 2 *Mean (± SD) of expired CO$_2$ output (ml /kg per min BTPS)*

Group	Time after delivery			
	15 min	*30 min*	*90 min*	*12–24 hours*
Controls	11·9 (1·4)	10·3 (1·6)	8·1 (1·4)	6·2 (0·8)
(Group 1, n = 19)	P<0·01	P<0·01		P<0·02
Maternal pethidine				
No antagonist (group 2, n = 24)	10·3 (2·3	9·1 (1·8)	7·8 (1·3)	5·7 (0·8)
	P<0·01)	P<0·02	P<0·001	
Nalorphine (group 3, n = 16)	12·6 (2·3)	11·1 (2·6)	8·7 (2·1)	6·1 (0·9)
	P<0·05	P<0·05		
Naloxone (group 4A, n = 14)	10·8 (1·6)	9·4 (1·1)	8·3 (1·1)	6·1 (1·1)
0·035 mg	P<0·01	P<0·05		
Naloxone (group 4B, n = 12) 0·07 mg	12·5 (2·1)	10·5 (1·5)	8·3 (1·2)	6·4 (0·8)

Table 3 *Mean (± SD) of alveolar ventilation (ml/kg/per min BTPS)*

Group	Time after delivery			
	15 min	*30 min*	*90 min*	*12–24 hours*
Controls	203 (42)	194 (50)	160 (47)	129 (29)
(Group 1, n = 19)	P<0·01			
Maternal pethidine				
No antagonist (group 2, n = 24)	163 (47)	165 (50)	142 (38)	118 (25)
	P<0·02	P<0·02	P<0·05	
Nalorphine (group 3, n = 16)	212 (70)	211 (78)	193 (83)	124 (30)
Naloxone (group 4A, n = 14) 0·035 mg	174 (48)	170 (43)	163 (39)	122 (27)
Naloxone (group 4B, n = 12) 0·07 mg	185 (35)	183 (36)	151 (32)	124 (27)

and 90 minutes with a smaller nonsignificant difference at 12–24 hours. Although the former were not statistically significant they do reflect a state of hyperventilation in group 3 compared with both the groups 1 and 2, and this was also manifest in a reduced capillary pCO_2 at 90 minutes.

After the lower naloxone dose in group 4A, CO_2 output and alveolar ventilation at 15 and 30 minutes were similar to those in group 2, indicating inadequate antagonism, and there was a significant reduction in CO_2 output ($P<0\cdot05$) in this group compared with the controls (group 1). However, there appeared to be a delayed naloxone effect with alleviation of respiratory depression at 90 minutes, the lack of statistical significance in this trend being due perhaps to the small number of cases.

In group 4B there was an improved initial antagonism. However, the values for alveolar ventilation (and capillary blood–gases) suggest that reversal of respiratory depression was not complete (Table 3). Compared with group 2, the CO_2 output was significantly higher at 15 minutes ($P<0\cdot01$) and at 30 minutes ($P<0\cdot05$) (Table 2). By 90 minutes the CO_2 output differences between groups 1, 2, and 4B were no longer significant but the values for both CO_2 output and alveolar ventilation suggested continuing antagonism.

In groups 2, 3, and 4 the alveolar ventilation values were correlated against the pethidine-to-delivery intervals of 0–1, 1–2, 2–3, and 3–4 hours. While there was obviously less respiratory depression in the 0–1-hour interval group, the differences were not significant, probably again due to the few infants in each group.

The results for the serial blood–gas analyses, the Brazelton and Scanlon scores, and the relation of alveolar ventilation to the pethidine-to-delivery intervals are not presented in full.*

The radioimmunoassay method was sensitive enough to enable naloxone levels to be followed for up to 4 hours after drug administration (Moreland *et al.*, 1979). Peak plasma levels of 4·0 to 20·2 ng/ml (mean 11·0) were observed during the first 40 minutes. Concentrations at the end of 4 hours ranged from 1·4 to 6·6 ng/ml (mean 4·2). In 4 newborn babies the drug concentration fell rapidly during the first 40 minutes and then declined more slowly, with an initial (distribution-phase) half-life calculated in one baby of 8 minutes. No such distribution phase was observed in the others and in 4 babies the plasma drug concentration increased during the first 20 to 40 minutes. The elimination-phase (mean ± SD) half-life calculated from all 12 newborn babies was 185 ± 108 min. The apparent volume of distribution determined by extrapolating the elimination phase curve was 1·99 ± 0·28 l/kg and the plasma clearance rate was 0·57 ± 0·12 l/kg per hour. There was no significant difference in the half-life, apparent volume of distribution, or clearance values between the newborn given 0·035 mg and 0·07 mg naloxone.

Discussion

The fact that relatively few cases were suitable for study during the 18 months of this project was due to the very strict criteria for selection, every effort having been made to eliminate all newborn babies with other depressant and complicating perinatal factors. During the study over 60% of the mothers received pethidine analgesia at some stage. The total dose received was relatively small and it was rare for a mother to be given a second dose, epidural anaesthesia being used if necessary. Despite this frequent but careful use of pethidine, our results confirm that significant depression of respiratory function was produced in these babies and, although slight, the differences were still apparent 12–24 hours after delivery. The fact that the effects of pethidine can be detected for even longer has been confirmed by Cooper *et al.* (1977) who found that it may take the newborn 3 to 6 days finally to eliminate the drug. Although not presented in detail, the respiratory function results were divided according to the pethidine-to-delivery time interval, and more obvious respiratory depression was found when the pethidine had been administered more than one hour before delivery.

Clinical assessments tend to be subjective and our preliminary observations of the state of wakefulness and of the sucking reflex were not performed under double-blind conditions. However, the pronounced excitatory effect of nalorphine was obvious and this confirms the clinical impression of hyperexcitability held previously. The Scanlon behavioural score, performed at 12–24 hours under double-blind conditions, indicated that there were no differences between the four groups. This differs from the findings of Brackbill *et al.* (1974), and may be due to the small numbers, to the timing, or to the subjective nature of the test. More objective tests such as those adopted by Wiener *et al.* (1977) to assess feeding, sucking, and habituation to an auditory stimulus are probably more accurate and reliable.

Nalorphine, although an effective antagonist to pethidine in terms of restoration of respiratory function, had an obvious excitatory effect, although it was not possible to estimate how much of the improvement was due to the narcotic antagonism and how much to stimulant effects. The most pronounced excitatory evidence of nalorphine was seen in the babies whose mothers had received pethidine within one hour of delivery, the group in which the babies were less likely to be depressed. No evidence of depressant effects of nalorphine were observed.

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*These may be obtained from J.E.H.B. on request.

Since this study was completed nalorphine has been withdrawn from the market, so naloxone is now the only neonatal narcotic antagonist. As expected, no agonist activity of naloxone in the two doses used was observed. However, the results suggest that the recommended IV dose (0·01 mg/kg) when given as a bolus injection into the cord is ineffective at 15 and 30 minutes in reversing pethidine-induced respiratory depression. The apparent delayed effect (at 90 minutes) of the smaller dose could be a random finding related to the fewer cases. A more probable explanation, and one compatible with data on naloxone plasma levels, is that the drug is retained in the umbilical vein and ductus venosus, so delaying the distribution into the systemic circulation.

An improved and more rapid effect was seen with the larger (0·02 mg/kg) dose which may have been flushed more rapidly into the systemic circulation because of the larger volume. The purpose of this work was to study the antagonists in the circumstances most likely to be found in everyday obstetric practice, so the effects of umbilical catheter or peripheral IV injection, which have practical disadvantages when dealing with the acutely depressed newborn, were not studied.

Evans *et al.* (1976) used alveolar pCO_2 in the calculation of alveolar ventilation, while we used capillary pCO_2 and it might be expected that the values in the two studies would differ slightly. Nevertheless, allowing for such differences in method, the general conclusions about the effects of IV naloxone are similar. Evans *et al.* (1976) and Wiener *et al.* (1977) studied IV naloxone at one dose only (0·04 mg) and our results support their finding that the effect of such a dose is transient, and they even suggest that the dose can safely be doubled. The results of a large IM dose of naloxone (0·2 mg) (Wiener *et al.*, 1977) are impressive, and demonstrate a prolonged effect. The values for CO_2 output (7·1–7·5 ml/min per kg) and alveolar ventilation (190·0–194·4 ml/min per kg) at 12–48 hours are very high compared with our own control values at 12–24 hours and with other reported figures (Nelson *et al.*, 1962). A large dose of naloxone may have an effect on respiratory function other than purely narcotic antagonism. The findings almost suggest that this massive dose is exerting an excitatory effect similar to that found in nalorphine-treated babies. This explanation is supported by the work of Bramwell and Bradley (1974) in which both nalorphine and naloxone were found to exert an effect at the locus for the excitatory effects of morphine. Whether levels of naloxone rise sufficiently rapidly after IM injection to obviate the need for an IV dose in the acutely depressed and asphyxiated newborn baby is still uncertain. Possibly the acutely depressed baby should be given an IV dose followed by a larger IM one.

The elimination-phase plasma half-life of naloxone in the newborn (3 hours) was considerably longer than that in the adult (one hour) (Ngai *et al.*, 1976). This is probably due to immaturity of the drug-metabolising enzyme systems in the newborn. This reduced rate of elimination after comparable dosage would be expected to lead to longer duration of action of naloxone in the infant compared with the adult, longer than the 30 minutes suggested previously (Evans *et al.*, 1976; Wiener *et al.*, 1977).

We confirm that large IV doses of naloxone, unlike nalorphine, do not have any obvious narcotic agonist activity in the newborn child. To produce rapid and effective narcotic antagonism, the recommended IV dose of naloxone could be safely doubled to 0·02 mg/kg and perhaps increased even more. As respiratory depression was detectable after treatment with antagonist, even in the entirely normal baby, it must be much more important to ensure adequate treatment in the asphyxiated, the preterm, or the otherwise at risk infant. The elimination-phase plasma half-life of naloxone after IV administration was about 3 hours, considerably longer than in the adult. Further studies are required to evaluate the most effective dosage, timing, and mode of administration.

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Creatine phosphokinase levels in the newborn and their use in screening for Duchenne muscular dystrophy

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SUMMARY The PKU sample, if taken after the 3rd day, is suitable for Duchenne muscular dystrophy screening using creatine phosphokinase (CPK) levels. 101 babies (53 girls and 48 boys) had CPK levels measured on filter paper blood specimens taken by heel prick on the 1st and 4th days of life. The method used was that described by Zellweger and Antonik (1975). The CPK levels were markedly raised on the 1st day of life but by the 4th day they had reduced to within 3 times the upper limit of the normal range for adults. 10 000 boys were then screened for Duchenne muscular dystrophy using the PKU sample, and 2 cases were found.

Duchenne muscular dystrophy (DMD) has a reported incidence of 1 in 3600 to 1 in 5600 live male births (Morton and Chung, 1959). It is inherited as an X-linked recessive condition and considered to be genetically lethal in boys as affected people do not reproduce. Calculations show that to maintain the incidence in the population, one-third of new cases with no family history must be fresh mutations. Thus carrier detection is very important for the mother and other female relatives.

The creatine phosphokinase (CPK) level is greatly raised in DMD, sometimes up to 30 or 40 times the upper limit of normal for adults. This led Zellweger and Antonik (1975) to suggest that screening of newborn boys for DMD could be carried out by measuring the CPK levels in the dried blood spots normally collected for PKU testing. Any persistent increases would be followed up by serum CPKs, clinical examination, and EMG studies. Early detection of affected infants identifies those mothers and female relatives who should be fully investigated to determine their carrier status before further pregnancies are considered.

The difficulty is that greatly increased CPK levels during the first few days of life have been found in normal newborn babies (Rudolph and Gross, 1966; Bodensteiner and Zellweger, 1971; Gilboa and Swanson, 1976). These increased levels have been attributed to birth trauma but no clear correlation has been established.

The aim of this study was (1) to investigate the blood levels of CPK in the neonatal period to establish whether blood taken on the 4th day (as used for PKU testing) would be satisfactory for DMD screening, and (2) to look at DMD screening in a defined population using the PKU specimen.

Methods

The population sample comprised 101 consecutive live births at St Helen's Hospital, Auckland, New Zealand. Two specimens (dried blood spots from heel pricks) from each infant were assayed; one had been collected within 24 hours of delivery and the other was one routinely taken for PKU screening on the 4th day. The CPK levels were measured using the 'CPK-screen' kitset (Antonik Laboratories) and a Chem-Glow photometer (American Instrument Company).

The CPK activity of the dried blood spot was expressed in arbitrary fluorescent units, in which one unit is equivalent to the meter reading on the Chem-Glow photometer using the 0–100 scale with multiplier switch in position 1. Capillary blood samples from 25 normal adults were collected on filter paper cards and assayed by the standard technique to establish a normal adult range. Data were also recorded about the pregnancy and delivery. Variables considered were birthweight, duration of 1st and 2nd stages of labour, number of pregnancies, maturity of fetus, and method of delivery.

10 000 consecutive liveborn male infants from the Auckland and Northland area were screened

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for DMD using the method described above. The specimens used were the PKU samples collected for the National Testing Centre. Greater than 20 SDs above the batch mean was taken as a positive result. Any positive result was retested, and if it was still greatly raised, a liquid blood sample was requested for a serum CPK estimation, and the baby referred to a paediatrician for evaluation. To investigate the possibility of false-negative results, those specimens with CPK levels outside 3 SDs of the mean of the batch were repeated and, if they remained raised, a 2nd dried blood specimen was requested.

Results

The CPK levels for all samples taken on days 1 and 4 are shown in Table 1. Analysis of day 4 levels gives a 95% confidence range of 13–77. This compared with an adult 95% confidence range of 3–34, and an adult mean of 18·5 with a SD of 7·9. Multiple regression analysis of the variables—birth weight, duration of 1st and 2nd stages of labour, number of pregnancies, and maturity of fetus—was carried out on the data obtained for those babies who were delivered vaginally (93 babies). The correlation coefficient of birthweight with the CPK level was 0·29 ($P<0.01$) and the correlation of the duration of 1st stage labour with the CPK level was 0·26. Multiple regression showed the correlation coefficient of both birthweight and duration of 1st stage of labour with the CPK level to be 0·36 ($0{\cdot}01<P<0{\cdot}05$).

Table 2 shows levels of CPK found for each method of delivery on days 1 and 4. This is further illustrated by the Figure. Statistical analysis of the CPK levels on day 1 showed a significant difference between vaginal and vaginal with forceps deliveries ($P<0{\cdot}01$), and between elective and emergency caesarean sections ($P<0{\cdot}02$). There was no significant difference between vaginal deliveries and elective caesarean sections ($t_{79} = 0{\cdot}6204$).

The 10 000 male infants screened showed a wide range of ages at which the PKU specimen was taken. An analysis by days of a random sample of 2217 out of the 10 000 is given in Table 3. The CPK levels found on day 2 were not significantly different from those found on day 3 or on day 4. Analysis showed that the negative regression of the CPK values on the age at which the PKU specimen was taken was not statistically significant.

Two greatly raised values were found—1400 and

Table 3 *Days on which the PKU specimen was taken*

Day	*No. (n = 2217)*	*Percentage*
2	8	0·4
3	493	22·2
4	866	39·1
5	527	23·8
6	137	6·2
7	78	3·5
8	34	1·5
9	23	1·0
10	15	0·7
11 +	36	1·6

Table 1 *CPK levels on the 1st and 4th days of life*

	Boys (n = 48)		*Girls (n = 53)*		*Total (n = 101)*	
	Day 1	*Day 4*	*Day 1*	*Day 4*	*Day 1*	*Day 4*
Mean	135·9	44·0	169·7	46·3	153·6	45·2
SD	87·2	16·7	191·9	15·6	151·7	16·0
Range	50–410	14–97	44–1150	18–90	44–1150	14–97

The CPK levels are measured in dried blood spots taken by heel pricks from 101 babies on the 1st and 4th days of life (PKU specimen). Units are arbitrary fluorescent units as described in text.

Table 2 *CPK levels on the 1st and 4th days of life for the different methods of delivery of the babies*

	Vaginal (n = 77)		*Vaginal and forceps* (n = 16)*		*Caesarean section*			
					Elective† (n = 4)		*Emergency (n = 4)*	
	Day 1	*Day 4*	*Day 1*	*Day 4*	*Day 1*	*Day 4*	*Day 1*	*Day 4*
Mean	136·9	45·1	252·2	45·7	92·5	48·0	141·5	42·0
SD	142·26	17·1	194·4	10·5	12·26	22·5	30·0	11·6
Range	44–1150	15–97	67–810	25–67	84–110	25–75	105–178	31–58

The CPK levels are measured in dried blood spots taken by heel pricks on the 1st and 4th days of life (PKU specimen). Units are arbitrary fluorescent units as described in text.
*Does not include Wrigley's forceps but does include Ventouse extraction; †all had had previous caesarean sections for difficulties in labour.

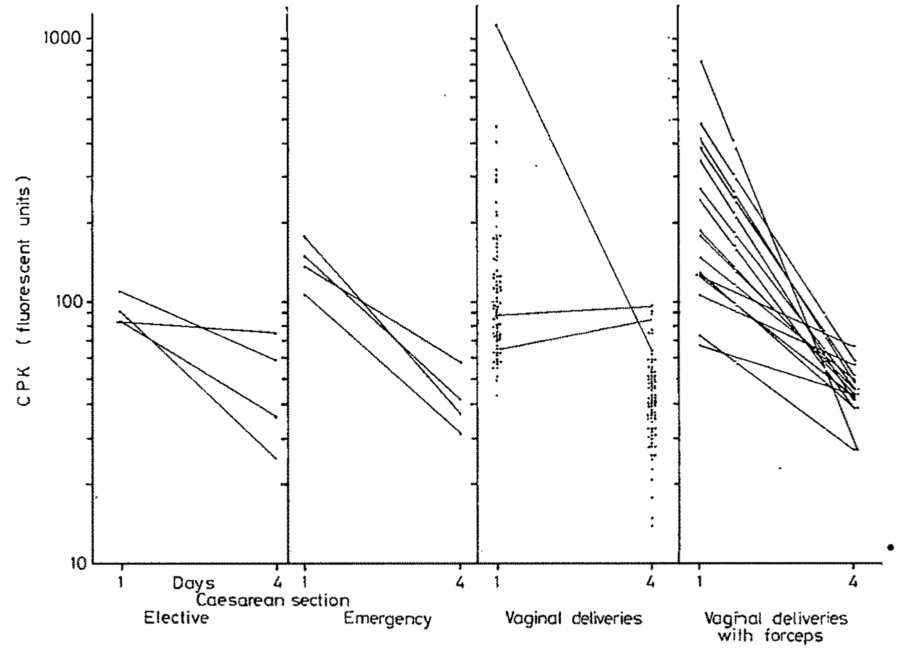

Figure *CPK levels (arbitrary fluorescent units as described in text) in dried blood spots collected on day 1 and day 4 from infants delivered vaginally with and without forceps, and by emergency and elective caesarean sections.*

1000 arbitrary units (PKU samples both taken on 4th day of life). These were respectively 161 and 94 SDs outside their batch means, and liquid blood specimens showed greatly raised serum CPK levels (3044 and 3000 IUs respectively). Physical examination of the two boys was normal. A muscle biopsy confirmed the diagnosis in one and, in both babies, the CPK remains at a greatly raised level. In neither case was there a history of DMD.

In the group of boys with CPK levels >3 SDs, one had on day 5 a CPK level between 5 and 6 SDs outside the batch mean but showed a greatly raised CPK at age 6 months. A liquid blood serum CPK level confirmed the greatly raised CPK levels (>2000 IU). On physical exmination the baby is normal and there is a family history of Becker muscular dystrophy.

Discussion

It has been suggested that the PKU blood sample would be ideal for DMD screening (Zellweger and Antonik, 1975; Beckmann *et al.*, 1976), but others feel that the CPK levels in the immediate neonatal period are too variable to make screening for DMD reliable (Gilboa and Swanson, 1976).

This study confirmed the variability of CPK levels in the 1st 24 hours but by the 4th day even greatly raised levels, as high as those associated with DMD (30 to 40 times the upper limit of normal adult range), had come down to within 3 times the upper limit of the normal adult range. The two highest levels found in two girls—1150 and 810—had reduced to 65 and 27 respectively by the 4th day. This confirms that if the PKU sample is taken after the 3rd day of life, the sample is suitable for DMD screening. As can be seen in the Figure, two CPK levels in the vaginal delivery category actually increased from day 1 to day 4, one from 66 to 86 and the other from 90 to 97. Both are still within 3 times the upper limit of normal for adults, and the increase can be explained by the error of the method. Triplicate determinations on 53 specimens showed the standard error of one measurement to be 8%. There was no significant difference in CPK levels between boys and girls on either day 1 or day 4. This would be in agreement with Demos (1971), who found no difference between boys and girls when he excluded boys with preclinical DMD.

The significant difference between CPK levels for normal vaginal deliveries and vaginal deliveries with forceps (not Wrigley's), and that between CPK levels for elective caesarean section and emergency caesarean section are indicative of difficult labour being associated with raised CPK levels. Rudolph and Gross (1966) suggest that hypoxia may damage the muscle cells and thus increase the CPK levels. There may be other causes of damage but the actual mechanism is still unclear. Birthweight and duration of 1st stage labour were the two birth variables that had a significant correlation with the CPK level, but this only explained 13% of the variations in CPK levels.

More significant factors may be the relationship between the configuration of the mother's pelvis and the baby's weight, the strength of uterine contractions and number and duration of periods of hypoxia, but these are very difficult to assess. It is interesting to note that in two cases, maternal pyrexia was present and the infants' CPKs on day 1 were 1150 and 470. This could be due to a viral infection in the child causing a myositis and thus raised CPK levels.

From the 10 000 babies tested, the incidence of DMD in the north of the North Island of New Zealand can be calculated to be 1 in 5000. This is comparable with the incidence estimated from the pooled data of Morton and Chung (1959) but lower than that found in Germany (Beckmann *et al.*, 1976).

The two DMD cases detected had CPK levels that were much higher than the values found for other infants. It seems there is a clear-cut distinction between 'normal' values for infants and values for preclinical DMD sufferers. However the milder X-linked Becker muscular dystrophy may not be detected by screening at an early age unless the threshold for a positive test is lowered to include a large number of false-positives.

In all three cases of confirmed muscular dystrophy, genetic counselling and carrier detection were offered. There was no family history in either case of DMD. Carrier detection studies were normal for one mother and abnormal for the other, so she intends limiting her family and having her only daughter tested when she reaches child-bearing age. Unfortunately the parents of these two cases of DMD are immigrants to New Zealand and their relatives live in Bermuda and Fiji where the carrier tests are probably not available.

The mother of the child with presumed Becker muscular dystrophy had normal carrier tests but only 60% of known carriers have raised CPK levels (Skinner *et al.*, 1975). She does not intend limiting her family as the two other affected family members have had only minor disabilities.

It has been suggested that parents wish to know about their child's condition as quickly as possible (Zellweger and Antonik, 1975; Beckmann *et al.*, 1976), but we found in the two DMD cases that this was not so. Information given at a very early stage may not be well received by parents. They are extremely upset and are concerned about their child who looks so normal. At this stage, they are less concerned about the outcome of future pregnancies. It appears that the people who replied to the questionnaires on whether they would like to know early about their child having DMD (Zellweger and Antonik, 1975; Beckmann *et al.*, 1976), are thinking of the practicalities of the situation and not of the emotional problems.

The problem of screening for DMD when there is no known cure has been discussed (*British Medical Journal*, 1975; Dubowitz, 1976). Gardner-Medwin (1976) points out that genetic counselling given after a DMD case has been detected by screening may not be as effective as predicted. In fact, Roses *et al.* (1977) suggest that the time and money would be better spent on research into the underlying cause of DMD and better carrier detection. In theory, screening and genetic counselling with carrier detection would reduce the incidence of DMD by preventing the birth of a 2nd case in a family. However it may be difficult for parents to make informed decisions when they have not adjusted to the fact that their 'normal' son has DMD. It will be interesting to see the long-term effect of screening and genetic counselling for DMD in places where such programmes have been well established.

Conclusions

1. The PKU sample taken on the 4th day of life can be used for DMD screening as the CPK levels in normal babies are low enough to distinguish from the levels found in DMD.
2. Difficult labours are associated with higher CPK levels.
3. Birthweight is a significant factor in raised levels of CPK, but the actual mechanism is still unknown.

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Serum 25-hydroxy-vitamin D in hepatobiliary disease in infancy

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SUMMARY Serum 25-hydroxy-vitamin D (25-OHD) concentrations were measured in 49 patients with hepatobiliary disease in infancy. Low mean values were found in groups of patients with biliary atresia, neonatal hepatitis, choledochal cyst, and chronic intrahepatic cholestatic syndrome. In the group of patients with surgically repaired biliary atresia, the mean value did not differ from normal. Parenteral vitamin D increased 25-OHD in serum in patients with biliary atresia, but did not do so in one patient with neonatal hepatitis. In contrast, oral vitamin D did not increase serum 25-OHD concentrations in patients with biliary atresia. It is concluded that the reduction of serum 25-OHD seen in biliary atresia was largely due to the malabsorption of vitamin D, while in neonatal hepatitis it was due to impairment of 25-hydroxylation of the vitamin.

Although rickets is a common complication in hepatobiliary disease in infancy (Yu *et al.*, 1971; Kobayashi *et al.*, 1974a), the mechanism underlying its pathogenesis is poorly understood. It can be postulated that the impairment of 25-hydroxylation of vitamin D in the liver may contribute to the pathogenesis of hepatic rickets. On the other hand, rickets in hepatobiliary disease may result from defective absorption of fat-soluble vitamin D because of deficient or absent bile flow into the intestine. The present study was undertaken to assess serum 25-hydroxy-vitamin D (25-OHD) concentrations in patients with hepatobiliary disease in infancy and to investigate the pathogenesis of hepatic rickets.

Subjects and methods

The subjects were 14 patients with biliary atresia, 22 with biliary atresia who had been successfully repaired by hepatic portojejunostomy and had no jaundice (Kobayashi *et al.*, 1976), 7 infants with neonatal hepatitis, 5 patients with chronic intrahepatic cholestatic syndrome, and one infant with choledochal cyst.

All patients with biliary atresia had laparotomy and the diagnosis was confirmed. Diagnosis of neonatal hepatitis was on clinical and laboratory grounds, excluding other diseases causing obstructive jaundice during infancy. Of 5 patients with chronic intrahepatic cholestatic syndrome, 3 had intrahepatic biliary hypoplasia (Alagille *et al.*, 1975) and the other 2 had recurrent intrahepatic cholestasis (Summerskill and Walshe, 1959). One infant with choledochal cyst had a laparotomy and the diagnosis was confirmed.

Radiological evidence of rickets was found in 7 (50%) of 14 patients with biliary atresia at the time of determination of serum 25-OHD. No lesions were observed in 22 patients with surgically repaired biliary atresias. In neonatal hepatis 3 (43%) of 7 patients had the lesion. In the group of patients with chronic intrahepatic cholestatic syndrome one patient with intrahepatic biliary hypoplasia had rickets. The infant with choledochal cyst had no radiological signs of rickets. The lesions in the present series were florid.

Serum 25-OHD was measured by a modified method of Belsey *et al.* (1974), using competitive protein-binding assay.

Results

Serum 25-OHD concentrations of control group. Serum 25-OHD was measured in 17 healthy infants and children. The mean value from age 2 months to 1 11/12 years was 22·4 ng/ml (n = 11, SD 9·5), with a range of 8·3 to 42·0. In the group above 2

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years of age it was 18·9 ng/ml (n = 6, SD 7·6), with a range of 12·5 to 30·0. There was no significant difference between the two age groups.

Serum 25-OHD concentrations in hepatobiliary disease (Fig. 1). In 14 patients with biliary atresia serum 25-OHD concentrations were conspicuously reduced with the mean value of 8·2 ng/ml (SD 5·2, range 2·0 to 17·5), which was significantly lower than normal ($P<0·001$). In contrast, the mean serum 25-OHD value for 22 patients with successfully repaired biliary atresia was 23·5 ng/ml (SD 11·0, range 6·0 to 43·5). The value was not significantly different from normal. In neonatal hepatitis the value was reduced to the same extent as in biliary atresia, with a mean of 9·2 ng/ml (SD 5·3, range 2·0 to 14·5). In chronic intrahepatic cholestatic syndrome serum 25-OHD was very low, with a mean of 6·4 ng/ml (SD 5·9, range 2·0 to 16·5). Patients with rickets generally showed low serum 25-OHD concentrations, while those whose serum levels were very low not always had radiological evidence of rickets. However, some of these patients with very low levels of serum 25-OHD and without rickets at the time of determination of serum 25-OHD, later showed radiological signs of rickets.

Effect of vitamin D on serum 25-OHD in hepatobiliary disease (Fig. 2). The effect of oral and parenteral vitamin D on serum 25-OHD was evaluated in 6 patients with biliary atresia. In 2 infants who had been given oral vitamin D 3000 IU daily, one for 2 and the other for 5 weeks, serum 25-OHD concentration did not change significantly (10·5 to 7·0, 13·5 to 13·5 ng/ml). In contrast, in 4 patients who had been given IM vitamin D 30 000 IU weekly for 2 to 12 weeks, serum 25-OHD concentration was enhanced, markedly in 2 (2·0 to 48·0, 7·5 to 27·0 ng/ml) and mildly in the other 2 (7·0 to 11·0, 15·0 to 18·0 ng/ml).

The effect of parenteral vitamin D on serum 25-OHD was evaluated in one infant with neonatal hepatitis in whom serum concentration before treatment was 2·0 ng/ml. On admission the patient suffered from tetany and haemorrhagic diathesis, while the stools were yellow in colour and serum bilirubin was 7·0 mg/100 ml (120 μmol/l). Serum 25-OHD was not raised, despite IM vitamin D 50 000 IU weekly for 2 weeks.

Comparative biochemical studies in hepatobiliary disease. The levels of serum alkaline phosphatase, calcium, magnesium, and phosphorus in each group were studied. Serum alkaline phosphatase level was raised in most patients with biliary atresia, neonatal hepatitis, or chronic intrahepatic cholestatic syndrome, and it was also raised in half of the patients with repaired biliary atresia. There was, however, no correlation between serum 25-OHD and alkaline phosphatase. Serum calcium levels were within the normal range in most patients with the

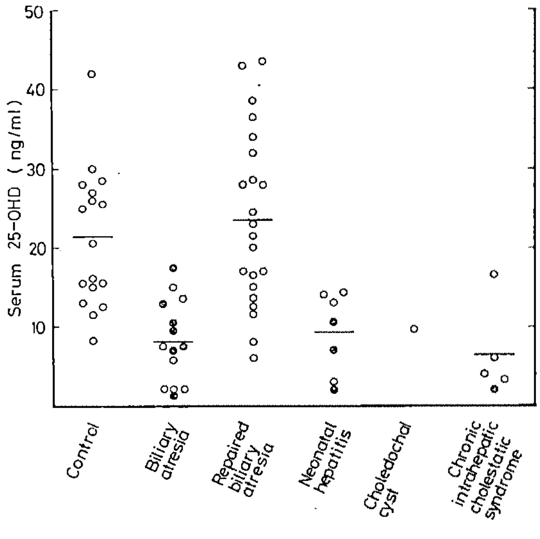

Fig. 1 *Serum 25-OHD concentration in hepatobiliary disease in infancy. Solid circles (●) indicate patients with rickets and open circles (○) those without the lesion.*

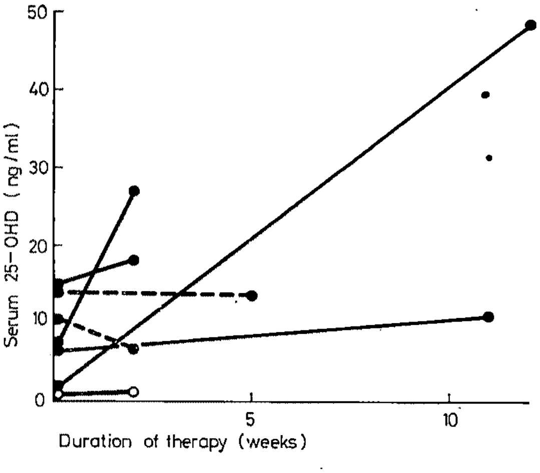

Fig. 2 *Serum 25-OHD concentrations in 6 patients with biliary atresia (●) and one with neonatal hepatitis (○) before and after treatment with oral (dotted lines) and parenteral (solid lines) vitamin D.*

Conversion: traditional units to SI—serum 25-OHD: 1 ng/ml ≈ 2·4962 nmol/l.

exception of 3 with biliary atresia, one with repaired biliary atresia, one with neonatal hepatitis, and one with intrahepatic biliary hypoplasia. Concentrations of phosphorous were within the normal range in all groups.

Serum 25-OHD did not correlate with any conventional liver function tests performed on these infants.

Discussion

There have been several reports on serum 25-OHD concentrations in adult patients with hepatobiliary disease, and the value is usually low (Haddad and Chyu, 1971; Hepner *et al.*, 1976; Long *et al.*, 1976; Wagonfeld *et al.*, 1976; Long *et al.*, 1978). However, we are unaware of any previous systematic survey of serum 25-OHD in infants with hepatobiliary disease. The present study showed low serum 25-OHD level in hepatobiliary disease in infancy, including biliary atresia, neonatal hepatitis, choledochal cyst, and chronic intrahepatic cholestatic syndrome. In biliary atresia, in which bile flow into the gut is absent, serum level was conspicuously reduced. In surgically repaired biliary atresia the value was enhanced to the normal range. In both neonatal hepatitis and chronic intrahepatic cholestatic syndrome serum 25-OHD was reduced to the same extent as in biliary atresia.

In the report by Daum *et al.* (1976), who studied serum 25-OHD in 5 cases of biliary atresia, the value ranged from 2 to 7 ng/ml. One case showed a normal level after surgical repair of biliary atresia despite the presence of secondary biliary cirrhosis. Their results were in general in accord with ours, but the range of the value in the present series was greater.

Our study showed that impaired 25-hydroxylation of vitamin D did not account for the low level of 25-OHD in biliary atresia, as serum 25-OHD was distinctly raised in at least 2 of 4 patients with biliary atresia who had received parenteral vitamin D. On the other hand, serum 25-OHD was not raised by treatment with oral vitamin D. These findings suggest that low serum level of 25-OHD observed in biliary atresia was attributable to the malabsorption of vitamin D rather than to the impairment of 25-hydroxylation of the vitamin. This conclusion accords with our previous report on the intestinal absorption of calcium and magnesium in hepatobiliary disease in infancy (Kobayashi *et al.*, 1974b). In the paper, it was shown that in biliary atresia parenteral vitamin D increased moderately the absorption of both elements, although oral vitamin D had little effect.

Rickets is a common complication in neonatal hepatitis (Yu *et al.*, 1971; Kobayashi *et al.*, 1974a), in which the malabsorption of calcium and magnesium has also been shown (Kobayashi *et al.*, 1974b). The present report showed a low serum level of 25-OHD in patients with the disease. The mechanisms underlying the pathogenesis of rickets in neonatal hepatitis, however, were different from those in biliary atresia. The impaired 25-hydroxylation of vitamin D may be responsible for the development of rickets in neonatal hepatitis to a greater extent than the malabsorption of vitamin D, as the present study showed that one infant who had been treated with parenteral vitamin D still had a low serum level of 25-OHD. This mechanism was also suggested by Antony and Beveridge (1975), who stressed the prematurity of infants with neonatal hepatitis. They stated that the small fat tissue and muscle mass of premature infants, the sites of storage for vitamin D, and the immaturity of hepatic enzymes in combination with hepatitis might have a role in the development of rickets.

From this study, and the previous one, it is reasonable to treat patients with rickets and biliary atresia with intramuscular vitamin D 30 000 IU weekly. In contrast, oral vitamin D is sufficient in mild or moderate cases of neonatal hepatitis in a dose of 2000 to 5000 IU daily for several weeks (Yu *et al.*, 1971), while infants with severely damaged liver parenchyma need oral 25-OHD, a more potent metabolite of vitamin D (Burmeister *et al.*, 1972; Daum *et al.*, 1976; Wagonfeld *et al.*, 1976).

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Relationship between urinary and blood glucose in diabetic children

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SUMMARY The relationship of urine glucose concentration with 'average' blood glucose concentration for the corresponding period was investigated in 10 juvenile diabetics during the performance of 15 inpatient metabolic profiles. 0% glycosuria was associated with 'average' blood glucose concentrations <6·4 mmol/l (<115 mg/100ml), 2% glycosuria with concentrations >8·6 mmol/l (>154 mg/100ml), and over 5% glycosuria with concentrations > 11·3 mmol/l (>204 mg/100ml). Urinary glucose loss was large (>278 mmol; >5g) when the 'average' blood glucose was >11·1 mmol/l (>200 mg/100ml). Because many diabetics have blood glucose concentrations up to 11·1 mmol/l, it is advantageous if glycosuria up to 5% is detectable by routine home urine tests. The 2-drop Clinitest method detects glycosuria up to 5% without significant loss of accuracy and is recommended in preference to the 5-drop method.

Diabetic control in children with diabetes is usually assessed by frequent measurements of urine glucose concentration. This test is performed by the child or his parents using a simple proprietary system. Clinitest tablets (Ames Company, Slough) are widely used and, in conventional use, 5 drops of urine plus 10 drops of water generate a colour indicating a reducing sugar concentration in the range from 0 to 2 g/100 ml (0 to 111 mmol/l). Alternatively, the 2-drop Clinitest method (Belmonte *et al.*, 1967) may be used; this uses 2 drops of urine plus 10 drops of water generating a colour range corresponding to a urinary-reducing sugar concentration from 0 to 5 g/100 ml (0 to 278 mmol/l).* Whichever system of urine testing is used, the urine glucose concentration is a retrospective and indirect measurement of the blood glucose concentration from the time that the bladder was last emptied. We studied the relationship between urinary and blood glucose concentrations measured over a 24-hour period in hospital in a group of diabetic children.

Methods

The study formed part of a larger investigation of metabolic profiles (N. K. Griffin *et al.* in preparation) performed on diabetic children to assess their total control. At the time of the study all the children were reasonably well controlled according to usual criteria. Informed consent was obtained from the children and their parents before admission to hospital, and throughout the study the children were on their normal diets and their physical activities were not restricted.

Fifteen 24-hour studies were performed on 10 children (3 girls and 7 boys). The ages of the children at the time of the study ranged from 10 to 16 years (mean 13·5) and they had been diabetic for 0·1–8 years (mean 4·2). All the studies were performed with the children on once-daily injections of insulin: 4 on Lente (unspecified manufacturer), 4 on Rapitard (Novo*), and 7 on Monotard (Novo*), with the daily dose ranging from 22 to 88 units (mean 47).

The patients were admitted to hospital in the evening and the study began the next morning. A plastic cannula was inserted into a peripheral vein and kept patent with heparinised saline between samplings. Blood samples were withdrawn for blood glucose measurements during the day before each main meal (7.30, 12.00, and 18.00 hours) and 15, 30, and 60 minutes after each meal. Samples were

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* Special colour charts for this colour range are available from Ames Company.

*Novo Insulins, Copenhagen, Denmark.

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also drawn before snacks (10.30, 15.00, and 20.30 hours) and during the night (23.00, 02.00, 05.00, and 07.00 hours). Samples for blood glucose were placed in 5% perchloric acid and the glucose subsequently measured using the hexokinase method (Bergmeyer, 1974).

Blood glucose measurements for each child were plotted against time and individual points were joined. From this line the blood glucose concentration was read at 30-min intervals throughout the 24 hours and the 'average' blood glucose concentration was calculated for each period between urine voidings.

Each urine sample voided was collected separately in plastic containers and the volume measured. An aliquot was placed in a separate fluoride tube, and the urine glucose concentration estimated using a glucose analyser with glucose oxidase (Analox Instruments).

The mean interval between voidings during the day was 2·7 hours (range 0·75–5). The overnight urine was passed as a single voiding in the morning: the mean time since the previous voiding for this specimen was 10 hours (range 8·5–11). The results of the overnight samples were analysed separately from the urine voidings and blood glucose measurements made during the day.

Results

Validation of the 2-drop urine test. 26 urine samples were tested for reducing sugar concentration using the 2-drop urine test and the corresponding glucose concentration was measured using the glucose analyser. The correlation is shown in Fig. 1. All but two Clinitest readings were accurate to within one colour reading on the 2-drop Clinitest scale but it was apparent that a reading on the Clinitest scale of 5% indicated a glucose concentration equal to, or greater than, 5 g/100 ml (278 mmol/l).

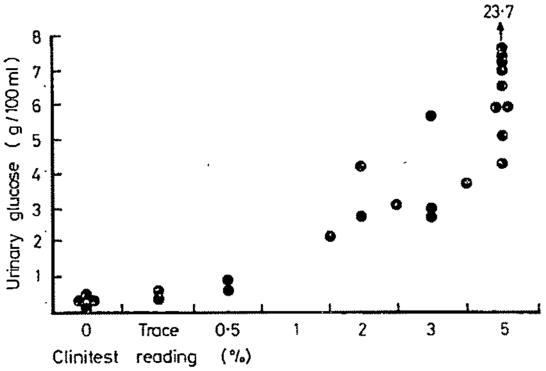

Fig. 1 *Correlation of the urinary glucose concentration measured by the glucose analyser and the Clinitest 2-drop method.*

Relationship between blood glucose concentration and urinary glucose concentration.

Night time period

There were 14 overnight urine collections. The relationship between the 'average' nocturnal blood glucose concentration and the urine glucose in the morning specimen is shown in Fig. 2. The correlation is poor and is not statistically significant.

Day time period

The relationship between the 'average' blood glucose concentration and the corresponding urinary glucose concentration during the day is shown in Fig. 3. The data relate to 10 children and represent 64 blood glucose/urine glucose pairs (r = 0·74; P<0·001).

Undetectable glycosuria occurred only with an 'average' blood glucose <6·4 mmol/l. 2% glycosuria indicated an 'average' blood glucose >8·6 mmol/l, and 5% glycosuria indicated a blood glucose >11·3 mmol/l.

The urine glucose excretion at each voiding was also measured. Fig. 4 shows that with an 'average' blood glucose <11·1 mmol/l (<200 mg/100 ml) the urinary glucose loss is small (<5 g; 278 mmol) but with >11·1 mmol/l considerable losses may occur.

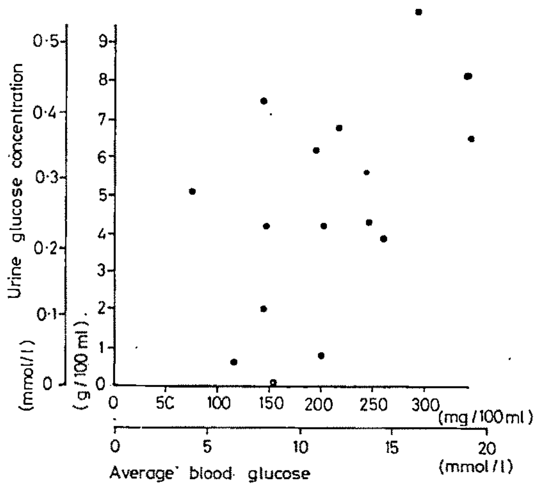

Fig. 2 *Relationship between the urinary glucose concentration in the first morning specimen and the 'average' nocturnal blood glucose concentration. The correlation is not significant.*

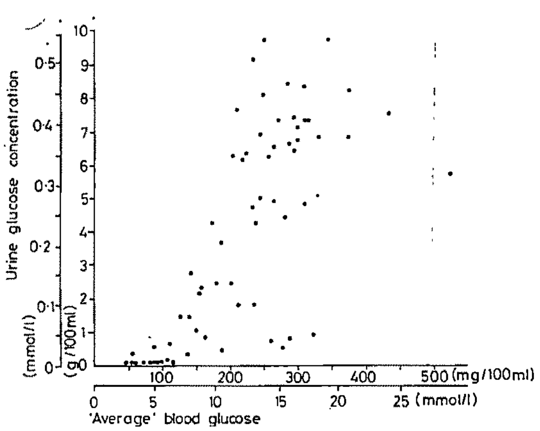

Fig. 3 *Relationship between the urinary glucose concentration and the corresponding 'average' daytime blood glucose concentration (P<0·001).*

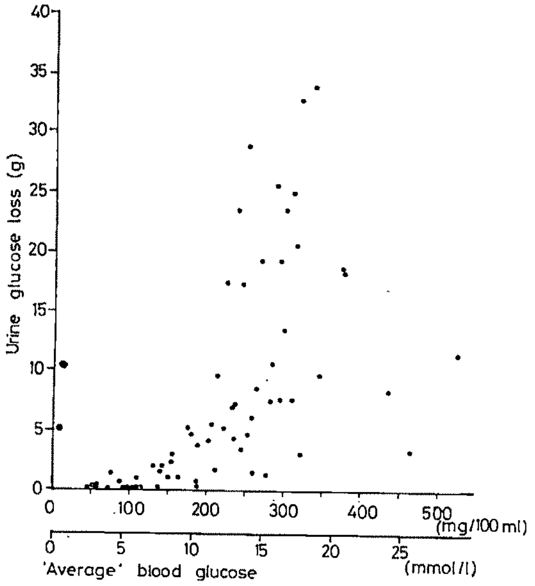

Fig. 4 *Relationship between the total urinary loss and the corresponding average daytime blood glucose concentration (P<0·001).*

Discussion

The day-to-day control of diabetic patients is currently judged principally on the urinary glucose concentration measured by the patient using a commercially available kit, such as Clinitest. In Britain the 5-drop method is often used but elsewhere the 2-drop method is more common. It is likely that urine testing will remain the primary index of diabetic control until systems for home monitoring of blood glucose (Sonksen *et al.*, 1978; Walford *et al.*, 1978) are simplified, especially in the case of diabetic children.

The usefulness of urinary glucose measurements in the management of diabetes depends on its accuracy in reflecting the blood glucose concentration. The two measurements are not constantly related as the urine glucose concentration will be influenced by the urine volume, the renal threshold for glucose, and the peak blood glucose levels reached between bladder voidings. These factors may alter from day-to-day because of variations in the patient's activity, fluid intake, and general health, and in qualitative changes in the carbohydrate eaten.

Overnight, changes in blood glucose concentrations occur more slowly but because of the longer time between bladder voidings they are not so accurately reflected by urinary glucose concentrations. The urine glucose may relate to the height of the postprandial blood glucose level the evening before, or to the rising blood glucose in the later hours of the night in patients in whom insulin activity does not completely cover 24 hours. It is, therefore, difficult to interpret the urine glucose concentration on the first specimen voided in the morning unless it is 0%.

During the day urine glucose concentrations give a valid retrospective index of blood glucose levels. Readings of 0% indicate a blood glucose concentration below the patient's renal threshold since the last urine specimen. Readings of 2% indicate an 'average' blood glucose >8·6 mmol/l, and levels of 5% indicate an 'average' blood glucose >11·3 mmol/l. Furthermore large quantities of glucose may be lost in the urine when the 'average' blood glucose is >11·1 mmol/l since the previous voiding (Fig. 4). In order to identify blood glucose concentrations of this level, urine glucose concentrations of 2–5% must be measurable. With Clinitest tablets this is only possible if the 2-drop method is used. The findings presented here confirm that the additional range of glycosuria detectable is of clinical value, and is achieved without any loss of accuracy at low levels of glycosuria.

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Iron deficiency in children with coeliac disease on treatment with gluten-free diet

Role of intestinal blood loss

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SUMMARY 24 children in whom coeliac disease had been diagnosed between one and 10 years earlier were re-examined for intestinal loss of iron and activity of the disease. Mild iron deficiency by laboratory criteria and by response to iron medication was common. The children with biopsy evidence of flat mucosa or intraepithelial lymphocytosis had a greater iron loss in their stools than those patients with normal, or almost normal, histology, The data suggest that loss of iron was mainly due to intestinal blood loss rather than to shedding of mucosal cells. We conclude that treatment with iron is indicated in many children with coeliac disease as the increased losses of iron persist for long periods although absorption of iron seems to improve or be negligibly affected.

Mild iron deficiency is often found in patients with coeliac disease being treated with gluten-free diets (Visakorpi *et al.*, 1970; Shmerling and Zimmerli-Häring, 1971). The potential aetiological factors are decreased absorption of iron, increased loss of iron with the rapidly turning over epithelium cells, and pathological bleeding through intestinal tract (Sutton *et al.*, 1970; Anand *et al.*, 1977; Harms *et al.*, 1977). However, impaired absorption is less likely to be the reason for iron deficiency as ferrous iron generally seems to be better absorbed after starting treatment (Badenoch and Callender, 1960; Anand *et al.*, 1977) and the absorption of haemoglobin iron, in particular, does not depend on the integrity of the mucosa of the proximal small bowel and is not reduced even in untreated patients (Webb *et al.*, 1967; Anand *et al.*, 1977).

We studied the role of intestinal loss of iron in a group of children with coeliac disease on long-term treatment with gluten-free diet, with or without evidence of active disease. This was done to obtain information on the pathogenic mechanism of iron deficiency and on the indications for treatment with iron.

Subjects

A group of 24 children (13 boys and 11 girls) with coeliac disease were re-evaluated. The initial diagnosis had been based on the presence of a flat proximal jejunal mucosa between 9 months and 10·7 years before the study (Interlaken agreement; Visakorpi, 1970). The patients had been treated by excluding gluten from their diet and were being followed up at least annually at this hospital. During this time, most of the patients had been given courses of iron when they were found to be anaemic. At the time of the study the children were aged between 3 and 17·2 years.

Methods

Hb and RBC indices were measured by a Model S Coulter Counter from venous blood drawn into EDTA. Reticulocytes were counted microscopically. A blood sample was also drawn in the morning for serum analyses. Serum iron and total iron-binding capacity were determined spectrophotometrically in duplicate (Bothwell *et al.*, 1972; Rice and Fenner, 1974) and transferrin iron saturation was calculated. Storage iron was estimated by serum ferritin assay in triplicate (Siimes *et al.*, 1974).

The patients with transferrin saturation $<16\%$

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and/or serum ferritin <1 μg/100 ml were started on treatment with iron; 2 mg ferrous iron/kg daily, given 1 to 2 hours before the meal. After a period of about 3 months the blood tests were repeated.

In 19 patients intestinal loss of iron was estimated by means of a 5-day stool collection 2 days after IV administration of 100 nCi ^{59}Fe Cl_3. The stools were then counted in a whole body counter with four detectors at 90° angles. The accuracy of the counting was ±20% in the activities of < 0·5 nCi, ±10% and ±7% in the activities of 1 and 2 nCi respectively. There are no control values from healthy children to indicate the physiological loss of iron by this technique. However, we have studied several children with severe iron deficiency anaemia and with suspicion of intestinal blood loss and found that presumed healthy children usually have <0·2 nCi (% of the injected label/5 days) in their stools. An arbitrary value of 0·5 nCi was used in this study as an upper limit of normal, although this value may be slightly too high.

In 5 additional patients daily stools were collected for between 7 and 10 days and analysed separately after giving the same dose of ^{59}Fe. The results of these counts were more accurate as there was only one stool container each day per measurement. The lowest detectable level of radioactivity was about 0·04 nCi.

In all 24 patients biopsy specimens were obtained from the first loop of jejunum using a Crosby-Kugler capsule of paediatric size; these were fixed in formalin, then routinely embedded, sectioned at 7 μm, and stained with haematoxylin and eosin. The histological findings were graded as total villous atrophy, partial villous atrophy, slight villous changes, and normal.

In order to obtain an additional and more sensitive quantitative criterion of the activity of the disease, the intraepithelial lymphocytes were counted in an area of the slide where the tissue was orientated, so that the plane of the section passed vertically through the epithelium and the basement membrane was easily visible. For each specimen at least 500 cell nuclei were counted. The results were expressed as the number of lymphocytes per 100 villous cells (Ferguson *et al.*, 1976).

The patients participated in this investigation voluntarily. The dose of radioactivity used was in accordance with the Scandinavian regulations on paediatric research (Radiation Protection Institutes in Denmark, Finland, Iceland, Norway, and Sweden, 1976)—i.e. a dose of less than the annual endogenous exposure.

Results

There was evidence of mild iron deficiency in the group of 24 children with coeliac disease. Hb, transferrin saturation, MCV of red blood cells, and serum ferritin were below the lower limits of normal in 6, 7, 6, and 8 patients respectively. However, anaemia was mild since the lowest Hb was 11·5 g/dl. The mean reticulocyte count was slightly raised. In 7 patients the values were above 1·5%, ranging from 1·6 to 2·3%.

A total of 10 children were considered to have iron deficiency by meeting at least two criteria denoting an abnormality. These patients were started on iron treatment, and later the laboratory values were all normal except in 2 of the 10 patients in whom the concentration of serum ferrin remained < 1 μg/100 ml. The mean levels of Hb, transferrin saturation, and serum ferritin rose from 12·6 to 13·4 g/dl, from 18·8 to 40·5% (P<0·01), and from 1·2 to 1·5 μg/100 ml respectively.

In 19 patients the mean amount of radioactivity in the 5-day stool specimens was 1·0 nCi (1·0% of injected dose) ranging from 0·2 to 3·0 nCi. In 17 of them the value was considered abnormal: 0·5 nCi or more. The daily excretion of radioactivity was measured in 5 other patients. The results are shown in the Figure.

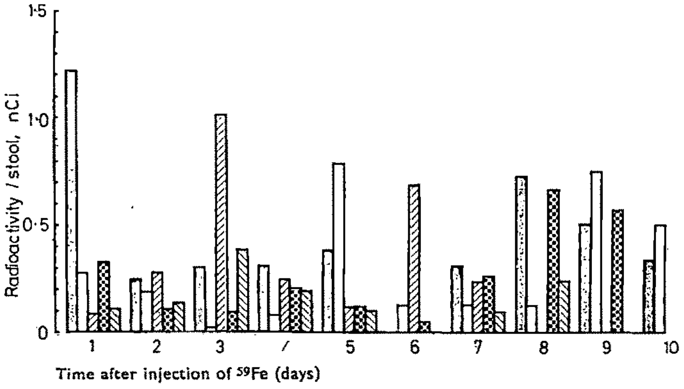

Figure *Radioactivity in stools of 5 patients collected daily after an intravenous injection of 100 nCi of* ^{59}*Fe* Cl_3*. Pattern of the secretion remained similar for 10 days, although there was a pronounced variation in individual stools from day to day. Each stool specimen contained some radioactivity. No specimen was obtained from 2 patients on day 6 and from some after 7 days.*

Abnormal proximal jejunal mucosa was found in 9 patients of whom 6 had total villous atrophy and 3 had only slight mucosal changes. The patients with flat mucosa had more radioactivity in their stools (from 1·2 to 3·0 nCi) than those with slight changes or normal mucosa (from 0·2 to 2·1 nCi).

In the patients with histological changes in mucosa the intraepithelial lymphocyte counts were high. The mean counts were 67, 55, and 32 and the total ranges from 51 to 87, from 44 to 64, and from 23 to 61 per 100 cells in patients with total villous atrophy, slight mucosal changes, and normal mucosa, respectively. The last range was also somewhat raised as in healthy individuals it is considered to be <34 (Kosnai and Kuitunen, 1977) or <38 lymphocytes/ 100 cells (Ferguson *et al.*, 1976). The intraepithelial lymphocyte count and the quantity of radioactivity in the stools showed a positive correlation in the 24 patients ($P<0·01$).

A negative correlation was found between the concentration of serum ferritin and the radioactivity in the stools ($P<0·001$).

Discussion

The results show a pronounced loss of radioactivity in stools after intravenous injection of labelled iron in a group of children with coeliac disease treated with gluten-free diet for at least one year. The loss could be attributed either to intestinal bleeding or to accelerated turnover of epithelial cells in which iron is lost in stools (Sutton *et al.*, 1970). Our results show that both mechanisms could be involved. However, the findings suggest that intestinal bleeding would account for a major proportion. The iron lost through epithelial cells should derive from serum and appear in stools during the first days after the injection, as the normally short turnover of these cells of about 3 days should be even more rapid in these patients. On the other hand, the incorporation of iron into haemoglobin starts immediately, and it is practically completed within 5 days. Accordingly, the radioactivity derived from red cells should gradually increase in the stools and then reach a certain plateau. It was evident that neither of these patterns was found. In addition, there seemed to be a pronounced variation in the loss of label from day to day in all patients.

The intestinal blood loss and signs of mild iron deficiency were greater in patients with total villous atrophy of the jejunum and in those with intraepithelial lymphocytosis. These findings suggest that iron treatment should be considered, for instance annually or semiannually, in these patients who are clearly unable to follow the dietary instructions. On the other hand, the patients who presumably kept to the diet more rigidly and who had a normal or almost normal mucosal histology also bled, although to a lesser extent. Some of these patients must therefore also have an increased need for iron, perhaps because some breaks in diet are inevitable even with strongly motivated families. Alternatively it is possible that subtle abnormalities in mucosal integrity remain, even with strict dietary management.

Several studies show that iron absorption is not a limiting factor in patients being treated for coeliac disease (Anand *et al.*, 1977). Our patients were able to compensate for most of the continuous loss of iron by increased absorption since any anaemia was mild. Patients with signs of iron deficiency responded well to iron, although they were unable to fill their iron stores as shown by the small change in concentration of serum ferritin (Siimes *et al.*, 1974). We feel that most children with coeliac disease require some iron. Reticulocytosis or reduced level of serum ferritin may be practical and sensitive criteria to detect these individuals.

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Absorption of chlorhexidine from the intact skin of newborn infants

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SUMMARY 34 newborn infants who had been bathed in a standard manner with Hibiscrub* were studied to find out whether it was absorbed percutaneously. Low levels of chlorhexidine were found in the blood of all 10 babies sampled by heel prick, and 5 of 24 from whom venous blood was taken. The detection of chlorhexidine varied greatly with the method and timing of sampling, and no correlation was found between gestational or postnatal age and chlorhexidine levels.

Antiseptic substances have been applied to the skin and umbilical cord stumps of newborn babies for many years with a view to controlling bacterial colonisation and reducing the prevalence of neonatal infection (Farquarson *et al.*, 1952; Williams and Oliver, 1969; Evans *et al.*, 1970; Gezon *et al.*, 1973; Dankert *et al.*, 1977; Fares *et al.*, 1977; Wald *et al.*, 1977). Hexachlorophane, a phenolic derivative effective against Gram-positive organisms, has been the most widely used. This substance is now known to be absorbed through the intact skin, particularly in preterm infants (Curley *et al.*, 1971; Powell *et al.*, 1973; Tyrala *et al.*, 1977). It has also been recovered from the brains of such babies, where it has been associated with a spongioform myelinopathy (Powell *et al.*, 1973; Shuman *et al.*, 1974, 1975). This has led to restriction in its use, particularly in infants of very low birthweights. Chlorhexidine, effective against Gram-positive and some Gram-negative bacteria (Lowbury *et al.*, 1964, 1974), appeared to be an appropriate substitute. It is not absorbed in any significant amounts from the hands of adults, even after prolonged use (Case *et al.*, 1976). As the skin of immature infants is known to be unusually permeable, this study was undertaken to determine the extent, if any, of chlorhexidine absorption.

Patients and methods

34 infants nursed in the neonatal intensive care unit at Hammersmith Hospital between November 1974 and January 1977 were studied. The purpose and nature of the investigation was explained to their mothers, who agreed to their infants' inclusion; the study also had the sanction of the hospital's ethical committee.

All babies in the study were 'topped and tailed' using water alone until the umbilical cord separated. They were then (or when size and general condition permitted) bathed daily with Hibiscrub used in a standard way throughout. A small quantity of the substance was applied with the bather's hand to the baby's head, excluding the face, and washed off with plain water. Chlorhexidine was then applied to the rest of the body, excluding any areas of broken skin; the infant was next immersed up to his neck in a bath of plain water, and then dried.

Blood samples were taken by heel prick or from a vein on the back of the hand (see below). The sampling site was swabbed with 70% isopropyl alcohol, mopped dry with sterile cotton swabs, reswabbed with isopropyl alcohol and allowed to dry. Blood was taken at the same time as samples needed for clinical purposes if possible. The whole blood sample was stored at 4°C until spun. Serum after separation was also stored at 4°C until analysed by gas-liquid chromatography after solvent extraction, acid hydrolysis, diazotisation, and iodination. A straight line was fitted to each set of calibration data by the method of least squares. Estimates for the unknown concentrations, together with their 95% confidence limits, were made by direct calculation from this fitted line. All esti-

*Hibiscrub is a detergent-based preparation containing 4% Hibitane chlorhexidine gluconate. Hibiscrub and Hibitane are trade marks, the property of Imperial Chemical Industries Limited.

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mated concentrations which gave negative values, or whose 95% confidence limits included zero, were considered as being not statistically significantly different from values obtained from blank samples. The numerical values, however, are included for completeness.

The gestational ages of the infants were calculated using the mothers' last menstrual periods and checked by a neurological and morphological scoring method (Dubowitz *et al.*, 1970). The 34 infants were divided into three groups.

Group 1 (10 infants). Blood samples were taken by heel prick at varying times after the first bath. Details of sexes, birthweights, gestational and postnatal ages are shown in Table 1.

Group 2 (7 infants). Samples were taken by venepuncture 4 hours after the first bath in case any measurable chlorhexidine in group 1 infants merely reflected adsorption of chlorhexidine on to the skin. Clinical details are shown in Table 2.

Group 3 (17 infants). Venous samples were withdrawn 12 hours after bathing and at weekly intervals if possible. These infants were studied to see if accumulation occurred and to attempt to see whether there was any correlation between gestational and postnatal ages and chlorhexidine blood levels. Details are shown in Table 3.

Results

Chlorhexidine was found in samples of blood taken from all 10 preterm infants in group 1 (Table 1). It was not realised, at this stage, that chlorhexidine is so strongly adsorbed on to the skin surface that it was not removed by the alcohol wash, so these results were almost certainly due to contamination of the sample by residual chlorhexidine on the skin. Where the concentrations were estimated as being negative these are shown as zero in the table.

Unlike the heel prick results, those recorded in venous samples were near the limits of detection of the assay and, therefore, some of the positive values could have been due to chance. Those that are considered to be significantly different from zero, based on the 95% confidence limits, are marked with an asterisk in the Tables and will be referred to as being significant in the following remarks.

While venous samples from infants in group 2 appeared positive in 6 of the 7 babies (Table 2), the three 'significant' values in this group were recorded in the 3 babies of 36 weeks or less. The infant who had no detectable chlorhexidine (Case 16) had an identical twin (Case 15) in whom 63 ng/ml was reported but, as this result does not differ significantly from zero, the 2 may have behaved identically with respect to absorption. The concentration of 460 ng/ml in Case 13 was very much higher than that in

Table 1 *Clinical details and total chlorhexidine in group 1 infants (capillary blood taken 1 and 4 hours after 1st bath)*

Case	*Sex*	*Birthweight (g)*	*Gestational age at birth (weeks)*	*Age at 1st bath (days)*	*Minimum chlorhexidine concentration (ng/ml)*	
					1 hour	*4 hours*
1	F	1140	28½	38	53*	21
2	F	1680	32½	11	79*	184*
3	F	1540	34	6	81*	134*
4	M	1800	34	10	380*	439*
5	M	2660	35	13	607*	1021*
6	M	2330	36	11	404*	67*
7	F	2240	36	5	260*	34
8	F	2360	37	17	539*	333*
9	M	2200	37½	9	75*	
10	M	2440	37½	9	251*	

*Denotes a result which is significantly different from zero.

Table 2 *Clinical details and chlorhexidine concentration in group 2 infants (venous blood taken 4 hours after 1st bath)*

Case	*Sex*	*Birthweight (g)*	*Gestational age at birth (weeks)*	*Age at 1st bath (days)*	*Chlorhexidine concentration (ng/ml)*
11	F	700	28	84	4
12	M	2030	33	6	101*
13	M	2440	35	7	460*
14	F	2180	35	7	169*
15†	M	1940	37	4	63
16†	M	2320	37	4	–56
17	F	3020	39	8	68

*Denotes a result significantly different from zero. †Identical twins.

Table 3 *Chlorhexidine concentrations in group 3 infants (venous blood taken 12 hours after baths on days stated)*

Case	*Sex*	*Birthweight (g)*	*Gestational age (weeks)*	*Age at 1st bath (days)*	*Chlorhexidine concentrations (ng/ml)*				
					Day 4	*Day 11*	*Day 18*	*Day 25*	*Day 32*
18	M	1350	29	52	7	0			
19	F	1470	30	18	21	214*	34		
20	M	1430	31	26	0	38	91*	0	
21	M	1640	31	11	4	64	4†		
22	F	1310	31	23	72	0	17		
23	F	1550	31	23	IS	16	IS		
24	F	1860	32	4	IS	0			
25	F	1470	32	26	0	0	0	0	
26	F	1830	32	6	IS	2	18		
27	M	1580	32	21	IS	0			
28	M	1540	33	10	0				
29	F	2100	33	8	0	1			
30	M	1870	33	8	2	19			
31	M	2140	34½	11	0	13			
32	M	2090	35	4	0	0			
33	M	1880	35½	2	0	IS	0		
34	F	2800	36	9	2	IS	7	28	31

*Significantly different from zero based on the 95% confidence limits; †baby not bathed in chlorhexidine for two days before this sample.
IS = insufficient sample.

the others in the group for no obvious reason. Postnatal age did not appear to affect the results.

When the results from the 17 infants from group 3 were analysed, only 2 significant positives were found. The percentage of significant positives was thus reduced from 95% in group 1, to 50% in group 2, and 5% in group 3. This would tend to confirm that at least some of the results in group 1 were owing to topical contamination with chlorhexidine. However, the only difference between group 2 (7 babies) and group 3 (17 babies) was that the samples were taken 4 hours after bathing in group 2 and 12 hours in group 3. It was not possible to detect any correlation between gestational–postnatal age and chlorhexidine levels in these groups, nor was there any tendency to accumulate the substance.

No unusual effects which could be attributed to chlorhexidine absorption were noted.

Discussion

This study was undertaken to ascertain whether chlorhexidine was absorbed through the intact skin of the newborn. It was prompted because hexachlorophane was in use as a bacteriostatic agent for more than 20 years before it was found to be absorbed (Curley *et al.*, 1971), and to be associated with spongioform lesions in the brains of monkeys and preterm babies bathed in it (Hart, 1971, cited by Lockhart, 1972; Powell *et al.*, 1973). The studies on hexachlorophane which led to these conclusions were undertaken when it was proposed to use hexachlorophane as a fungicide on fruit and vegetables.

The results reported from our survey show that chlorhexidine is detectable in the blood of some preterm and term infants after whole body bathing. Although there were more positive results in preterm babies, these were too few for statistical analysis. Percutaneous chlorhexidine absorption would not be surprising as many other substances are absorbed in this way, particularly in the neonatal period. These include hydrocortisone, trichlorocarbanilide, pentachlorophenol, and, of course, hexachlorophane (Fisch *et al.*, 1963; Feinblatt *et al.*, 1966; Armstrong *et al.*, 1969; Robson *et al.*, 1969). Nachman and Esterly (1971) demonstrated skin blanching with phenylephrine hydrochloride 10% in preterm but not term babies, thus confirming increased permeability in the immature. As any substance to which newborn skin is exposed may be absorbed to some extent it is a question of balancing its value against potential risks. There are differing views on the effectiveness of, or even the necessity for, topically applied antibacterial substances in newborn babies (Forfar *et al.*, 1968; Evans *et al.*, 1970; Gezon *et al.*, 1973; Light and Sutherland, 1973; American Academy of Pediatrics Committee on Fetus and Newborn, 1974; *British Medical Journal*, 1977; Dankert *et al.*, 1977), but it is beyond the scope of this paper to review opinions on this controversial subject.

There are no reports yet of any tissue toxicity due to chlorhexidine, but necropsy studies have not been made. Despite the extensive use of chlorhexidine in obstetrics, ear, nose, and throat surgery, in dentistry, and as a preoperative disinfectant, the only adverse reactions reported in adults have been associated with direct instillation into the middle ear, where in common with other antiseptics, it causes deafness. However, adults absorb virtually no chlorhexidine from the skin, even after prolonged use (Winrow *et* *al.*, 1973). Newborn rhesus monkeys bathed daily with chlorhexidine digluconate showed no clinical evidence of toxicity (Case *et al.*, 1976). Rats given chlorhexidine in their drinking water for 2 years showed no ill effects in life or at necropsy although there were easily detectable levels of chlorhexidine in the liver and kidney (Case *et al.*, 1976). It has been shown to cause concentration-dependent precipitation of rat liver microsomal protein, probably due to RNA binding and possibly to membrane binding too; and it binds rat liver microsomes affecting various enzyme systems in them (Christensen and Jensen, 1974; Christensen *et al.*, 1975). These effects were noted on subcellular fractions exposed directly to high concentrations of chlorhexidine, and all were thought to be related to the cationic amphipathic nature of chlorhexidine. Pharmacologically chlorhexidine is a biguanide, and the related substances phenformin and metoformin exert their metabolic effects by inhibiting fatty acid oxidation at toxic doses; they also inhibit oxidative phosphorylation (Muntoni, 1974).

With regard to the prime object of this study which was to demonstrate whether chlorhexidine is absorbed from the skin of newborn infants, the possibility of its adsorption to skin makes interpretation of results from heel prick samples inconclusive. When blood was obtained by venepuncture, however, small amounts of chlorhexidine were found in the blood of a few babies tested. Some of the most immature infants in this study were several weeks old when first bathed with chlorhexidine, so their skin permeability would already be less than at birth. Should further work be undertaken, sampling technique and postnatal age at exposure must be taken into account, and the use of chlorhexidine in obstetric units remembered.

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The following articles will appear in future issues of this journal:

Ring 20 chromosome in a child with seizures, minor anomalies, and retardation. *J. M. Stewart, N. Cavanagh, and D. T. Hughes.*

Acute intermittent porphyria and epilepsy. *R. Biagini, R. Tignani, A. R. Fifi, and L. Nappini.*

Comparative trial of manual and mechanical persussion technique with gravity-assisted bronchial drainage in patients with cystic fibrosis. *M. Maxwell and A. Redmond.*

Dubin-Johnson syndrome with some unusual features in a Chinese family. *N. S. Lo, C. W. Chan, and J. H. Hutchinson.*

Use of growth hormone gel. *B. Lippe, S. D. Frasier, and S. A. Kaplan.*

Changing incidence of neonatal hypermethioninaemia: implications for the detection of homocystinuria. *P. D. Whiteman, B. E. Clayton, R. S. Ersser, P. Lilly, and J. W. T. Seakins.*

Archives of Disease in Childhood, 1979, **54**, 384–390

Infective pericarditis in Nigerian children

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SUMMARY 53 children with infective pericarditis were seen at the University College Hospital, Ibadan, between 1967 and 1976. Their ages ranged from 10 days to 15 years but 53% of them were aged 5 years and below. Cough, fever, and breathlessness were the most common symptoms; cardiac decompensation was evident in over 30% of them, 23% had muffled heart sounds, but a pericardial friction rub was audible in only one. The main pathogens identified were *Mycobacterium tuberculosis* (11 cases), *Staphylococcus aureus* (11 cases), *Escherichia coli* (4 cases), *Pneumococcus* and *Pseudomonas* (3 cases each). Most of the patients had some other associated infection—such as, bronchopneumonia (12 cases), empyema thoracis (10 cases), lung abscess (10 cases), septicaemia (6 cases), and osteomyelitis (3 cases). Errors in diagnosis were common, the diagnosis having been missed in 72% of the cases identified at necropsy. Even if the correct diagnosis had been made during life and appropriate treatment given, the mortality rate (36%) was high. It is suggested that the onset of cardiac failure in any child with bronchopneumonia, empyema, or lung abscess should always arouse a suspicion of infective pericarditis.

Studies by many workers from developed countries on infective pericarditis suggest that this disorder is a rarity in childhood (Horan, 1957; Boyle *et al.*, 1961; Nadas and Levy, 1961; Benzing and Kaplan, 1963; Gersony and McCracken, 1967; D'Cruz *et al.*, 1970; van Reken *et al.*, 1974). Few studies on pericardial diseases have been undertaken by workers from the developing countries and these have concerned mainly adults (Schrire, 1964; Brockington and Edington, 1972; Carlisle and Ogunlesi, 1972; Brockington, 1974; Odi Assamoi *et al.*, 1975). To our knowledge there has been one study on pericardial diseases from Africa on children and adults and this suggested that infective pericarditis is more common among children in the developing countries than in developed ones (D'Arbella *et al.*, 1972). The purpose of the present study is to document the prevalence, clinical features, aetiological factors, and prognosis of infective pericarditis seen at the University College Hospital, Ibadan, during a period of 10 years.

Materials and methods

The study was prospective as well as retrospective. The prospective aspect comprised 14 children with infective pericarditis referred to the paediatric cardiac unit between January 1967 and December 1976. Clinical diagnosis of infective pericarditis in 11 of the 14 patients was confirmed by diagnostic pericardiocentesis which in each case yielded pus. The pericarditis in the remaining 3 children was of tuberculous origin, as confirmed by the pericardial exudate, a strongly positive tuberculin test, and satisfactory response to treatment with anti-tuberculous drugs. All 14 children underwent detailed evaluations, and their nutritional states were assessed from their weights, heights, mental states, muscle mass, subcutaneous tissues, and skin changes. Investigations carried out on each child were: blood count, haemoglobin genotype, culture of blood, pericardial or pleural aspirates, electrocardiography (ECG), and chest radiography. One patient underwent venous angiocardiography.

The retrospective study comprised 39 cases identified at necropsy during the same 10-year period. The necropsy diagnosis of these 39 cases was based on widely accepted criteria (Scotti, 1971). The clinical, laboratory, and necropsy findings of these patients were also reviewed.

Cases of pericarditis associated with cardiothoracic

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surgery, uraemia, malignancies, collagen disorders, endomyocardial fibrosis, or idiopathic cardiomegaly were excluded from the study. It should also be emphasised that the present series may not represent all the cases of infective pericarditis that passed through the hospital during the period as some of the patients might not have come to our attention.

Results

There were 53 patients (28 boys and 25 girls) and their ages ranged from 10 days to 15 years (mean 5·3 years). Two (4%) of them were neonates, 26 (49%) were between 1 month and 5 years, 16 (30%) between 6 and 10 years, and 9 (17%) were aged between 11 and 15 years.

Symptoms and signs. The commonest presenting symptoms were fever, cough, and breathlessness (Table 1). Five of the older children complained of retrosternal chest pain while 3 others, all aged less than 5 years, had febrile convulsions. Cardiac decompensation, as evidenced by tachycardia, weak peripheral pulses, raised jugular venous pressure, gallop rhythm, or hepatomegaly was present in over 30% of the children. Less than 25% of patients had muffled heart sounds, and pericardial friction rub was present in one. Kussmaul's sign was demonstrable in only one patient.

Nutritional state. Complete data on the nutritional state were available in 37 (70%) of the 53 patients. 10 (27%) of these 37 patients were marasmic while the remaining 27 (73%) were well nourished.

Chest radiography. Enlargement of the cardiac silhouette was present in 22 (82%) out of 27 patients in whom the cardiac borders were clearly discernible. Three of these 22 patients with enlarged cardiac silhouettes had constrictive pericarditis of tuberculous origin. In one of the 22 patients pericardiocentesis yielded very little purulent aspirate in spite of clinical, radiological, and ECG signs of a large pericardial effusion. In order to assess the amount of the effusion a jugular venous angiocardiogram was carried out and it showed a large amount of pericardial fluid (Fig. 1). Another interesting chest *x*-ray which posed some diagnostic problem was that of an 11-month-old girl who presented with a history of fever, cough, breathlessness, and a swelling in the neck. On examination she was pyrexic (39°C) and had signs of cardiac failure and a left pleural effusion. In addition she had a tender and fluctuant mass which seemed to arise from the thoracic inlet. Although the mass did not move with swallowing, it increased in size whenever the child cried. The chest *x*-ray showed a large globular heart and a wide superior mediastinal shadow (Fig. 2). Diagnostic paracentesis of the left pleural cavity, pericardial space, and the cervical mass yielded pus. Post-paracentesis chest *x*-ray showed pneumonediastinum with the air extending into the soft tissue in the neck.

Table 1 *Symptoms and signs in 53 children with infective pericarditis*

Symptoms	*No. of patients*	*% of total*	*Signs*	*No. of patients*	*% of total*
Fever	39	74	Pyrexia	53	100
Cough	35	66	Tachycardia	45	85
Breathlessness	28	53	Dyspnoea	36	68
Abdominal swelling	12	23	Hepatomegaly	35	66
Swelling of legs	12	23	Weak peripheral pulses	21	40
Anorexia	7	13	Pulmonary crepitations	21	40
			Splenomegaly	20	38
Swelling of face	6	11	Peripheral oedema	19	36
Vomiting	6	11	Mucosal pallor	19	36
Chest pain	5	9	Raised jugular venous pressure	18	34
Diarrhoea	4	8	Muffled heart sounds	12	23
Vomiting	4	8	Ascites	10	19
Convulsions	3	6	Gallop rhythm	6	11

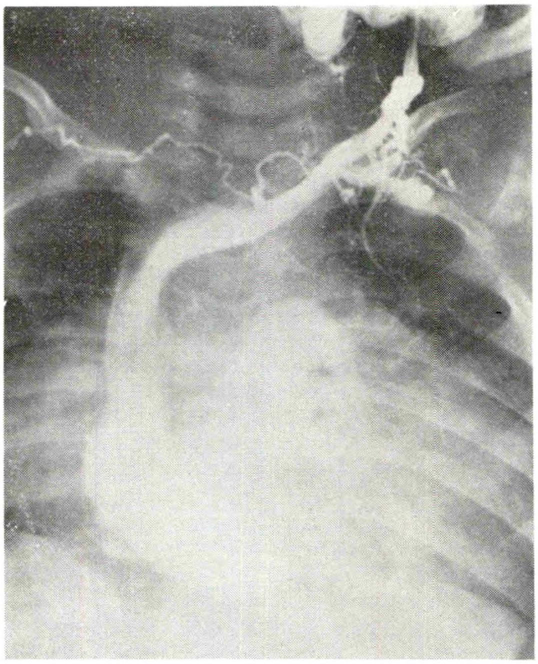

Fig. 1 *Percutaneous venous angiocardiogram of a baby with purulent pericarditis. The pericardial effusion is demarcated on the right side by the opacified right atrium and the outer border of the cardiac silhouette.*

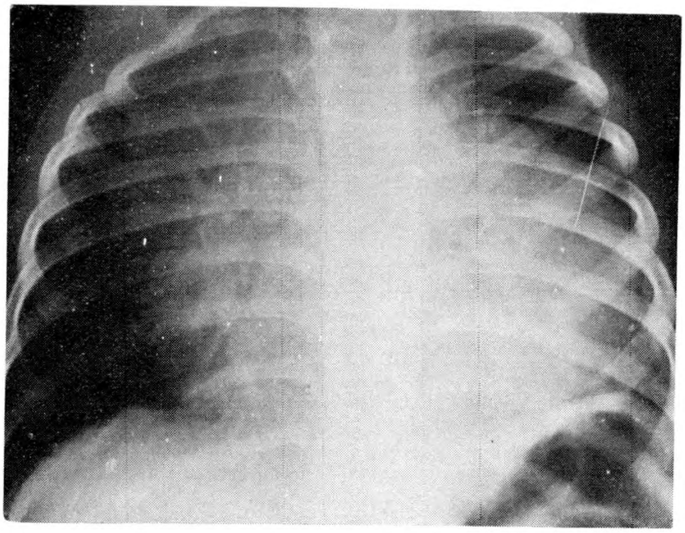

Fig. 2 *Chest x-ray of an 11-month-old child with pyopericardium and pyomediastinum. Note the soft-tissue shadow in the superior mediastinum.*

It was thus concluded that the cervical abscess was an extension of a large pyomediastinum. Satisfactory recovery followed drainage of the pus collections and administration of erythromycin, digoxin, and hydroflumethiazide.

Other radiographic findings were bronchopneumonic consolidation (12 cases) and pleural effusion (10 cases). The pleural effusion was on the left side in 7 patients, on the right in 2 others, and bilateral in one. Pericardial calcification was evident in one patient with purulent pericarditis.

Electrocardiographic findings. Electrocardiograms were obtained in all 14 patients studied prospectively and in one of the necropsy cases. Flat or inverted T-waves, the commonest abnormalities, were observed in 10 (67%) of the 15 patients while 7 (47%) patients had dwarfed QRS complexes. Other ECG abnormalities included S-T depression (4 cases), bifid P-waves (2 cases), and frequent but unifocal ventricular premature contractions (1 case).

Aetiological agents. Aetiological agents were identified on Gram-stain and cultures either of the aspirates or blood in 31 (58%) of the 53 patients. The commonest nontuberculous pathogens were *Staphylococcus aureus*, *Escherichia coli*, *Pneumococcus*, and *Pseudomonas aeroginosa* (Table 2). These organisms were isolated from the blood (6 patients), pericardial aspirates (9 patients), and pleural aspirates (4 patients). Three of the 4 patients with *E. coli* pericarditis were aged less than one year. Eight patients had histological evidence of tuberculosis in pericardial specimens obtained at necropsy while in 3 others the diagnosis of tuberculosis was made before death. Guinea-worm was identified in the pericardium of one patient at necropsy.

Table 2 *Aetiological agents*

Pathogen	*No. of cases** ($n=36$)	*% of all isolates*
S. aureus	11	31
M. tuberculosis†	11	31
E. coli	4	11
Pneumococcus	3	8
P. aeroginosa	3	8
Klebsiella sp.	2	5
Salmonella typhi	1	3
Dracunculus medinensis (guinea-worm)	1	3

*4 patients each had more than one pathogen: (i) *S. aureus*, *Pseudomonas*, and *Klebsiella*; (ii) *S. aureus* and *Pneumococcus*; (iii) *Pneumococcus* and *Klebsiella*; (iv) *E. coli* and *Pseudomonas*.
†Histological proof only.

Haematological findings. Total white blood counts were available in 19 patients, 14 (74%) of whom had a polymorphonuclear leucocytosis (neutrophils $>7{\cdot}0 \times 10^9/l$; 7000/mm^3). Anaemia (haematocrit $<25\%$) was present in 6 out of the 19 patients whose haematocrits were available. The haemoglobin genotype was determined in 21 patients; it was A in 18 patients, and A+S in 2 others. One patient had haemoglobin SC disease.

Associated conditions. 20 (38%) of the 53 patients either had empyema thoracis or an extensive lung abscess (Table 3). Five patients had both empyema and lung abscesses. The bronchopneumonia which was present in 12 patients was presumed to be bacterial in origin. Less common associated conditions were pyogenic meningitis, acute bacterial

Table 3 *Associated conditions*

Associated disease	*No. of cases*	%
Bronchopneumonia	12	23
Metastatic abscess (<2 cm in diameter)		
Lungs	7	
Brain	2	21
Kidney	2	
Empyema thoracis	10	19
Extensive lung abscess	10	19
Tuberculosis		
Pulmonary	4	
Meningeal	2	
Disseminated	2	17
Spinal	1	
Septicaemia	6	11
Osteomyelitis	3	6

endocarditis, myocardial abscess, omphalocele, congenital hydronephrosis, and left ventricular submitral aneurysm (one case of each).

Pathological types. 22 (42%) of the 53 patients had purulent pericarditis (Table 4); 13 of these 22 patients had some other intrathoracic suppurative lesions. Three patients with purulent pericarditis developed fatal cardiac tamponade, and at necropsy each of them had >300 ml pus in the pericardial cavity. 11 patients had serious pericarditis: 4 cases were tuberculous while the remaining 7 were idiopathic. Six of the 7 cases of contrictive pericarditis were also of tuberculous origin; the aetiology of the 7th case was unknown.

Antemortem diagnosis. Pericarditis was not suspected during life in 28 (72%) of the 39 cases identified from necropsy records; in most instances only the associated pulmonary infection was accurately diagnosed. Even when cardiac failure was recognised, as indeed was the case in 7 (25%) of the 28 cases, it was usually ascribed either to idiopathic cardiomyopathy or to acute cor pulmonale resulting from pneumonia or empyema.

Treatment and outcome. The 14 patients studied prospectively were managed with appropriate antibiotics, drainage of pus collections, digoxin, diuretics, and blood transfusion in appropriate cases. Five (36%) of the 14 patients died; 4 of them had purulent pericarditis and one had tuberculous pericarditis. Thus the mortality rates were 36 and 33% respectively for purulent and tuberculous pericarditis. Age, sex, nutritional state, or duration of the illness before hospitalisation did not appear to affect the mortality. In 2 of the 5 fatal cases there was an associated large lung abscess and a massive empyema in 2 others. The 9 survivors have been followed up for periods varying between 18 months and 4 years. Eight of them have recovered completely (Figs 3a, b) while the remaining patient has persistent cardiac decompensation.

Table 4 *Types of pericarditis in 53 children*

Type	*Patients* *(n=53)*	%
Fibrinoid pericarditis	5 (1)	9
Effusive		
Serous	11 (4)	21
Purulent	22	42
Haemorrhagic	3	6
Adhesive pericarditis	5	9
Constrictive pericarditis	7 (6)	13

Figures in parentheses denote proportion of cases that were of tuberculous origin.

Discussion

The present series of 53 cases of infective pericarditis seen during a period of 10 years in children aged 10 days to 15 years is in accord with the 62 cases reported from Uganda by D'Arbella *et al.* (1972) in patients aged 0–20 years. In contrast, Simcha and Taylor (1971) reported only 5 cases seen at The Hospital for Sick Children, London, between 1952 and 1970. Workers from different parts of North

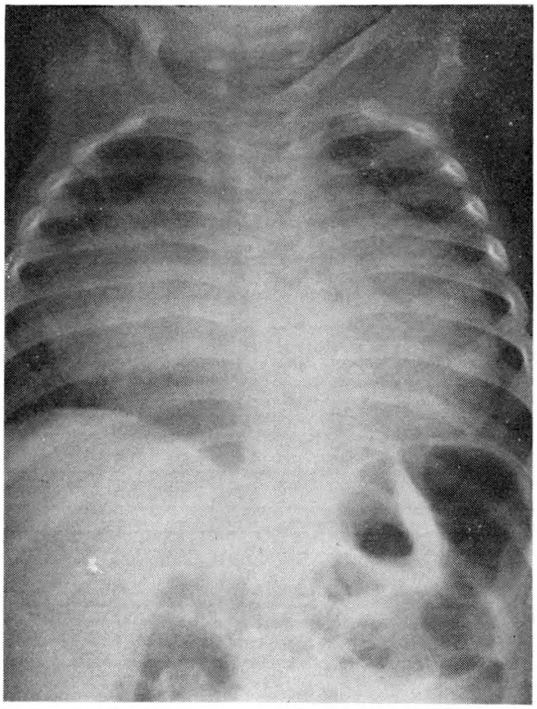

Fig. 3a *Chest x-ray of a baby with purulent pericarditis; the cardiac silhoutte is enlarged and globular.*

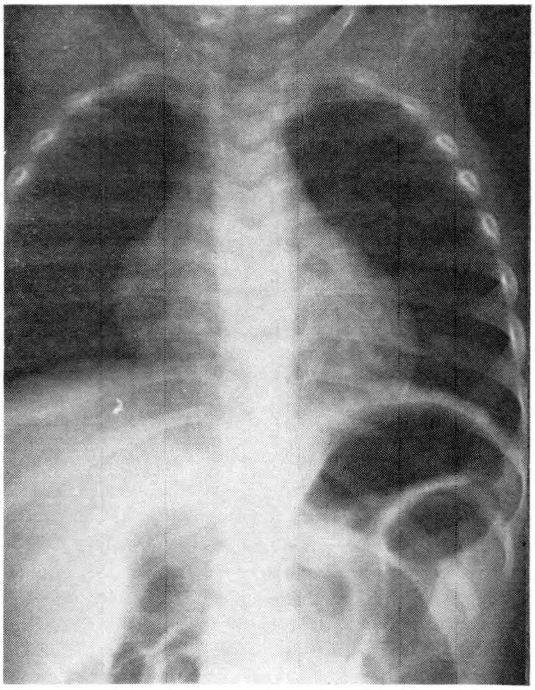

Fig. 3b *Same patient as in Fig. 3a, 4 weeks later. The cardiac size had returned to normal after pericardial drainage and administration of antibiotics, digoxin, and diuretics.*

America (Benzing and Kaplan, 1963; van Reken *et al.*, 1974; Strauss *et al.*, 1975; F. Jaiyesimi, unpublished data) have also stressed the rarity of infective pericarditis in childhood in these developed countries. It may thus be concluded from the present series, and that of D'Arbella *et al.* (1972) from Uganda, that infective pericarditis is a more common childhood disease in the developing countries than in developed ones. Poor sanitation, widespread malnutrition with its depressing effects on immune mechanisms (Chandra, 1972; Dossetor *et al.*, 1977), and the high incidence of bacterial respiratory infections (Abdel-Khalik *et al.*, 1938; Mimica *et al.*, 1971; Aderele, 1977; Silverman *et al.*, 1977), no doubt contribute to the high prevalence of infective pericarditis in children living in developing countries; but infective pericarditis is by no means a major childhood health problem in such countries. For example, it accounted for only 6% of paediatric cardiac disorders (A. U. Antia and F. Jaiyesimi, unpublished data), and for less than 1% of total paediatric admissions into University College Hospital, Ibadan, during this 10-year period. Similarly, during the same period 2079 necropsies were carried out on children aged 15 years and below, and the incidence of infective pericarditis was 0·02%.

In the present as well as in other series (Horan, 1957; Al-Omari and Samarrai, 1971; D'Arbella *et al.*, 1972; van Reken *et al.*, 1974; Odi Assamoi *et al.*, 1975) *S. aureus* was the most common aetiological agent. This organism has also been reported to be the commonest infectious agent in other conditions in our hospital (Aderele *et al.*, 1974; Montefiore *et al.*, 1974; Jaiyesimi, 1977). *E. coli* was the next most common pyogenic organism and this may be related to the number of infants in the present series. It is worth noting that the aetiological agent was unknown in 41% of the patients in the present study. D'Arbella *et al.* (1972) also reported a high incidence of idiopathic cases in their series. This high incidence of idiopathic cases may be attributed to several factors. Firstly, antibiotics might have been administered before the patients' admission into hospital. Secondly, a low index of suspicion would result in many cases being unrecognised and thus in failure to institute appropriate investigations. Thirdly, in most of our patients no virological studies were carried out.

Several workers have stressed the ease with which cases of infective pericarditis are unrecognised before death (Poynton, 1908; Poynton, 1934; Horan, 1957; Boyle *et al.*, 1961). In the present series the diagnosis was missed in 72% of cases that came to necropsy. This high incidence of misdiagnosis may be due to the nonspecific nature of the presenting symptoms and the scarcity of characteristic signs. For instance, a pericardial rub is audible in only 15 to 25% of cases (Benzing and Kaplan, 1963), while the intensity of the cardiac sounds may be normal in the presence of cardiac tamponade (Williams and Soutter, 1954; Nadas and Fyler, 1972). Occasionally some of the characteristic signs may be obscured by those of a coexisting bronchopneumonia, lung abscess, or empyema, as was indeed the case in most of our patients. Similarly, the clinical diagnosis of effusive tuberculous pericarditis is fraught with pitfalls: the same globular, 'murmurless' heart may be due to endomyocardial fibrosis and the pericardial fluid chemistry may be similar in both endomyocardial fibrosis and tuberculous pericarditis (Antia, 1968; Somers *et al.*, 1971). In such clinical situations a right ventriculography may be the only method of differentiating between these two conditions.

The spectrum of associated conditions in the present series is similar to that described by previous authors (Boyle *et al.*, 1961; Benzing and Kaplan, 1963; van Reken *et al.*, 1974). However, the extensive pyomediastinum which was found in one patient has not, to our knowledge, been previously reported.

The factors which have been reported to have adverse effects on the prognosis in purulent pericarditis are overwhelming infection (Horan, 1957), and inadequate evacuation of the pus within the pericardial cavity (Al-Omari and Samarrai, 1971). In the present series prognosis appeared to have been adversely affected by septicaemia, coexisting suppurative lung disease, and misdiagnosis with failure to institute appropriate treatment. Rooney *et al.* (1970) suggested that prognosis in tuberculous pericarditis might be adversely affected by delay in diagnosis and treatment, as well as by the mechanical constraints which pericardial inflammation imposes on myocardial compliance. As only 3 of our prospectively-studied patients had tuberculous pericarditis we cannot make any valid statements on the prognosis in that category of patients.

The failure to recognise many cases of infective pericarditis before death highlights the need for a high index of suspicion on the part of clinicians, particularly those who practise in the developing countries where the disease is relatively more common. The onset of cardiac failure in any child with bronchopneumonia, empyema, or lung abscess should always arouse a suspicion of purulent pericarditis. In addition to frequent clinical and radiographic evaluations, a diagnostic pericardial tap should be mandatory in all such patients; and a venous angiocardiogram may be required occasionally to demonstrate a loculated pericardial effusion. The need for these invasive procedures, however, can be obviated by echocardiography, this being a non-invasive and perhaps the most sensitive method of detecting pericardial effusions (Feigenbaum *et al.*, 1966; Moss and Bruhn, 1966; Feigenbaum, 1972; Meyer and Kaplan, 1972). Furthermore the ease with which echocardiography can be repeated renders it invaluable in assessing the course of a pericardial effusion.

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Change of reference style

From January 1980, the *Archives* will change its style for citing references and will follow the number system. We are making this change in order to conform with the 'Vancouver style' of uniform requirements for manuscripts submitted to biomedical journals.

Previously the *Archives* has used the Harvard reference system. Its advantages and disadvantages compared with those of the number system have seemed evenly balanced, but the editors have been aware of the burden imposed on authors and their secretaries by the different styles which different journals require. Therefore, with the unanimous agreement of the editorial committee, we have decided to support a move whereby a large—and increasing—number of major medical journals will accept manuscripts presented in one agreed style.

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From now onward all manuscripts submitted should accord with the new style.

[1] International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979; **1**; 533–535.

[2] Lancet. The Vancouver style. Uniform requirements for manuscripts submitted to biomedical journals. *Lancet* 1979; **1**; 429–430.

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Short reports

Comparison of IV salbutamol with IV aminophylline in the treatment of severe, acute asthma in childhood

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SUMMARY A double-blind test to compare IV aminophylline with salbutamol in the treatment of acute, uncontrolled asthma showed that both drugs were equally effective during the first 24 hours. Salbutamol caused a relative tachycardia. Hydrocortisone was given after 2 hours, but did not appear to affect the rate of recovery.

A double-blind test was undertaken to compare aminophylline with salbutamol given intravenously to children admitted to hospital with acute, uncontrolled asthma. 18 children (12 boys and 6 girls) were studied, age range 1½ to 7 years. All were considered to be sufficiently ill to require intensive hospital treatment on clinical grounds. Blood-gases on admission were attempted in all children and obtained in 13. Of these, 12 showed hypoxaemia, 5 showed acidaemia, and one showed hypercapnoea. Using random number tables the children were allocated to receive double-blind either salbutamol 4 µg/kg immediately then 0·6 µg/kg per hour continuously for 24 hours or aminophylline 4 mg/kg immediately then 0·6 mg/kg per hour continuously for 24 hours. In 2 children the initial dose of bronchodilator was omitted because both of them had received bronchodilator treatment during the 4 hours before admission. After 2 hours all children received hydrocortisone 4 mg/kg immediately then 2 mg/kg per hour continuously for 22 hours. All patients were offered oxygen via face masks.

The study took place during the first 24 hours of admission. The children were assessed according to their clinical signs, pulse rates, and respiratory rates at 1, 2, 4, 6, 12, 18, and 24 hours. Clinical signs were

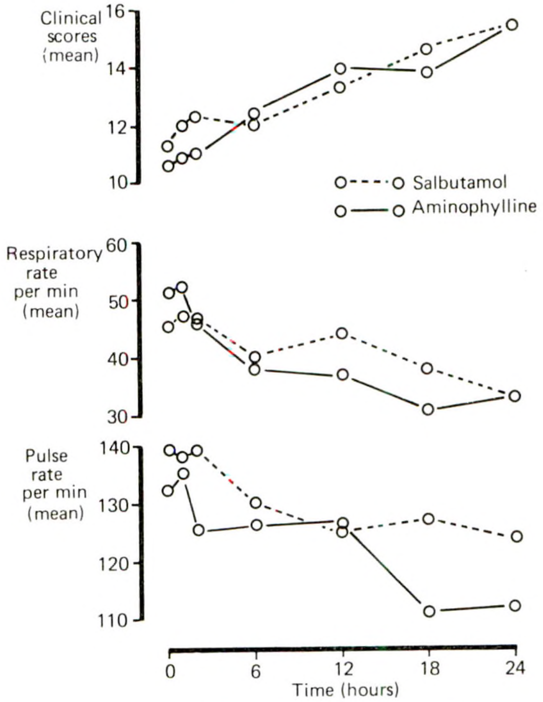

Figure *Mean values of pulse rates, respiratory rates, and clinical scores during first 24 hours.*

Table *Scoring system for signs*

	Score			
	4	*3*	*2*	*1*
Recession	Nil	Intercostal	Intercostal + suprasternal	Intercostal + suprasternal + lower costal
Tracheal tug	—	Nil	Present	Pronounced
Air entry	Normal	Reduced	Barely audible	Absent
Rales	—	Nil	Occasional	Widespread
Rhonchi	Nil	Scattered	Widespread, numerous	Concerted (= wheeze)

scored according to the method shown in the Table, a modification of the method used by Pierson *et al.* (1974).

Results

Pulses, respiratory rates, and clinical scores are shown in the Figure. No child showed any significant deterioration after starting treatment, and the condition of all children improved steadily after one or two hours. No statistically significant difference (Student's *t* test) between the aminophylline and salbutamol groups was found, except for pulse rates at 18 and 24 hours, when salbutamol appeared to cause a relative tachycardia.

Discussion

Clinical signs improved in all children from starting treatment, and pulse and respiratory rates improved after 2 hours. All children were unequivocally better at 6 hours. Their improvement during this period can be largely attributed to either salbutamol or aminophylline. Although the children received hydrocortisone after 2 hours, it is unlikely that this drug began to have any effect for several hours (Collins *et al.*, 1970, 1975). Furthermore our data give no indication that there is a precise time at which recovery is accelerated after the administration of hydrocortisone. The results are similar to those of Pierson *et al.* (1974) who carried out a study in which hydrocortisone appeared to ameliorate hypoxaemia immediately, but did not affect any other parameters in this way.

Salbutamol caused a tachycardia seen at 18 and 24 hours, but the clinical significance of this is trivial. No patient suffered any cardiac arrhythmia.

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Adder bites in children

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SUMMARY 16 children with adder bites were admitted to hospital in Southampton in the years 1969–77. Two children were severely poisoned; these 2, and a 3rd, fulfilled suggested criteria for antivenom administration but they recovered without it. Three children had no treatment, and 9 children no analgesia. Prolonged morbidity was not seen in these children. Careful observation in hospital was the most important factor in management, with early clinical improvement obviating the need for antivenom.

Children are less likely to suffer long-term morbidity after snake bites than adults, but can suffer no less severely from the immediate consequences of the venom. Experience in Southampton shows that snake bites to children are not uncommon, although Reid (1976) suggested they were rare. Controversy still exists about the use of antivenom, particularly in children. The experience with children bitten by *Vipera berus*, and admitted to hospital in Southampton is reviewed.

Patients

A retrospective study was made of all children, aged 14 years or younger, admitted to hospital in Southampton with a diagnosis of adder bite during the 9 years 1969–77. The diagnosis was accepted if the observed signs were compatible, whether or not a snake was seen. Postdischarge morbidity was ascertained by writing to the families; most of the children were visitors to the area, making follow-up difficult.

During the period 1969–77, 16 children (14 of whom were boys) were diagnosed on clinical grounds as having suffered a snake bite (a snake was not seen in 2 cases), and admitted to hospital. They ranged in age from 14 months to 14 years. All but one incident occurred within the New Forest area of Hampshire in the months June, July, or August. The one exception was a boy who kept snakes for a hobby and was bitten at home in April (Case 15). Eight children were bitten on the leg or foot, 7 were bitten on the hand, and one on his ear as he lay in the grass.

Results

Details of the clinical findings and subsequent course are given in the Table.

Immediate effects. Pain from the infliction of the bite was the first symptom in most children, but one child complained initially of a painful, swollen foot (Case 9). The 14-month-old baby (Case 2) was alleged by his parents to have lost consciousness for 5 minutes shortly after the bite, but this may have been a breath-holding attack. Vomiting occurred in 4 children: in two within a few minutes (Cases 6 and 13), and in Cases 8 and 15 within 30 minutes of the bite.

Features on admission. Most of the children were seen in hospital within an hour of the bite, with the exception of Case 12 who sought help the next day. Those in whom envenomation had occurred displayed the characteristic signs as shown in the Table. Six children were thought to be only mildly poisoned, pain and swelling being slight. Another 5 were moderately severely poisoned, with swelling of the bitten limb. Only 2 were severely poisoned; the history of one is given below (Case 8).

It was thought envenomation did not occur in 3 children (Cases 2, 10, and 11), although characteristic fang marks were easily identifiable in each case. The following case reports illustrate the course of events in 2 children.

Case reports

Case 13. A 9-year-old girl vomited within minutes of being bitten on the right ankle. When seen in casualty department an hour later ankle oedema was noted. No systemic signs were noted; her BP was 90/65 mmHg. She needed pethidine to control severe pain. Within 2 hours bruising covered the

Table *Details of 16 children admitted to hospital with adder bites*

Case	*Sex*	*Age (years)*	*Bite*			*Drugs**	*Days in hospital*	*Severity of poisoning*
			Date	*Site*	*Effects*			
1	M	9	7/1969	L. foot	Pain + +, oedema, bruising, adenitis + +, infection	Promethazine, papaveretum, codeine, paracetamol, erythromycin	8	Moderate
2	M	14/12	8/1969	L. ear	Bite mark, loss of consciousness	None	2	Nil
3	M	8	8/1969	R. ankle	Oedema, bruising, adenitis + +	Promethazine	6	Moderate
4	F	8	6/1973	R. hand	Oedema, bruising	Aspirin, hydrocortisone	2	Mild
5	M	5	6/1974	L. finger	Oedema	None	1	Mild
6	M	10	7/1974	L. finger	Oedema, vomiting	Hydrocortisone, erythromycin, chlorpheniramine, aspirin	6	Moderate
7	M	11	7/1974	R. thumb	Oedema, haemorrhagic blister	Hydrocortisone, promethazine, chlorpheniramine, ampicillin, paracetamol	5	Moderate
8	M	3½	6/1975	R. foot	Oedema, bruising, lymphangitis, vomiting, pain, hypotension	Hydrocortisone, chlorpromazine, chlorpheniramine, pethidine, pentazocine	9	Severe
9	M	4	7/1975	R. ankle	Oedema, bruising adenitis + +	Hydrocortisone	3	Mild
10	M	9	7/1975	L. calf	Blister, induration	Hydrocortisone, chlorpheniramine	1	Nil
11	M	5	7/1975	R. ankle	Bite marks	Hydrocortisone	1	Nil
12	M	6	7/1975	L. ankle	Oedema	Hydrocortisone	2	Mild
13	F	9	7/1976	R. ankle	Vomiting + +, pain + +, oedema, bruising	Chlorpheniramine, pethidine, phenoxymethylpenicillin	3	Moderate
14	M	7	8/1976	R. finger	Oedema, bruising	None	2	Mild
15	M	14	4/1977	R. hand	Vomiting, pain + +, oedema + +, moderate hypotension	Hydrocortisone, phenoxymethylpenicillin, promethazine, pentazocine	3	Severe
16	M	13	8/1977	R. hand	Oedema	Chlorpheniramine		Mild

*All children received tetanus toxoid.

dorsum of the foot and ankle. Investigations showed a raised total white blood count ($17 \cdot 0 \times 10^9$/l); a slightly raised blood urea (8 mmol/l; 48·2 mg/100 ml); slight acidosis (HCO_3 20 mmol/l); a raised creatine phosphokinase (CPK 253 IU/l, normal <80 IU/l). She was treated with chlorpheniramine and penicillin V and the leg was kept in a raised position. 14 hours later oedema had spread to the thigh. Throughout, her BP remained stable. Her recovery was uneventful and she was discharged after 3 days.

Case 8. A 3½year-old boy became pale, lethargic, and vomited 30 minutes after being bitten on the right foot. When seen in hospital less than an hour later, the foot was oedematous. He was given hydrocortisone and transferred to Southampton. 90 minutes after the bite he was still pale and vomiting, with a recorded systolic BP of 50 mmHg. Bruising covered the foot, and inguinal nodes were already very tender. He was still hypotensive (45/20 mmHg) 4½ hours after the bite. Chlorpromazine was given to control vomiting, and chlorpheniramine for the rapidly developing oedema. Severe pain required pethidine initially, then pentazocine. Six hours after the bite his BP had returned to normal. At 16 hours swelling had reached the inguinal region. Thereafter his recovery was slow but uneventful, and he was discharged on the 8th day.

Treatment. All the children received tetanus toxoid; in 3 children this was the only medication. Pain was severe enough in 3 children to require narcotic analgesics, but 9 required no analgesia. The other drugs given are shown in the Table.

In no case was Zagreb antivenom used, although it has been available in Southampton since 1972.

Sequelae. All children made a complete recovery. The average length of stay in hospital was 3·4 days (range 1–9). Most children were virtually symptom-free at discharge, but Cases 13 and 14 were in discomfort for a further week, and Case 7 was lethargic for about 2 weeks.

Discussion

Experience gained by hospital admission of 16 children bitten by adders in one small area of the country during the last 9 years adds to our knowledge about their management. Although these 16 comprise all the children who presented at hospital in Southampton, it is not possible to comment on children who managed without medical help, or who presented at their local hospitals; one child in this series (Case 12) presented the day after being bitten.

In this series most of the children suffered no more than acute discomfort in a swollen, bruised limb. Three children were probably not poisoned; about 30% of snake bites fail to envenom (Henderson and Dujon, 1973).

In moderate poisoning it is likely that no treatment is required other than symptomatic therapy, usually analgesics and antiemetics. The use of antihistamines can be limited to those in whom angioneurotic-type oedema appears (Reid, 1976); it did not occur in the present series. Prednisone is of no value in the treatment of the more severe Malayan viper bite (Reid *et al.*, 1963).

Three children gave cause for anxiety (Cases 8, 13, and 15), particularly the 2 boys with hypotension. All 3 had early indications for the administration of Zagreb antivenom (Reid, 1976; D.A. Warrell, 1976, personal communication), but they recovered without it. Reid's indications include persistent or recurrent hypotension, a leucocytosis $>20 \cdot 0 \times 10^9$/l, metabolic acidosis, ECG changes, raised CPK values, and in adults, the presence of massive swelling within 2 hours of the bite. Warrell would also include neurological abnormalities, bleeding diatheses, and massive swelling within 4 to 6 hours, in children as well as adults.

Transient hypotension lasting 4 to 12 hours is common in severe venom poisoning: it lasted 6 hours in Case 8 and 5 in Case 15, and did not recur. Had the condition of either of them deteriorated or the hypotension persisted after 12 hours, antivenom would probably have been given. Case 13 had investigation abnormalities. From the criteria of Reid (1976), these indicated that antivenom should have been given, but as the patient was in a reasonably good clinical state, it was withheld pending further observation.

No child developed early massive swelling. Reid's reason for this being an indication for antivenom in adults is to reduce the period of morbidity, which can last several months. Prolonged morbidity is not a problem with children and these data confirm this. Warrell adds that early massive swelling indicates a large envenomation, and therefore an increased potential for cardiotoxicity; hence he includes children. This, however, he bases on his experience with puff-adders; it is not a reported problem with *Vipera berus*.

Conclusions

Some risk is inherent in many forms of treatment, particularly if the material is immunogenic. Zagreb antivenom, being a foreign protein, is in this category. Nevertheless it has been shown to combine efficacy with safety in monkeys (Theakston and

Reid, 1976), and there is no reason to believe it is less safe in humans. Antivenom has not yet been used in Southampton although 3 children might well have received it if the criteria (Reid, 1976; D. A. Warrell, 1976, personal communication) had been wholly accepted. However early clinical improvement showed that it was not necessary.

When there is a successful outcome one can accept that the clinical decisions were correct; the difficulty lies in deducing future management. Guidelines for the administration of Zagreb antivenom are reasonable, but if acted upon too early in children, may lead to unnecessary administration. In Southampton a policy of symptomatic treatment in hospital and careful observation has been safe. Zagreb antivenom remains available for the serious cases that do not show early improvement.

I thank Professor I. C. S. Normand, Dr M. Radford, and Dr C. F. Speirs for their advice and criticism.

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Coeliac disease in identical twins

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SUMMARY Coeliac disease occurred at the same age in MZ twins. The diagnosis was confirmed by histology of the small intestine, rapid response to a gluten-free diet, and relapse after reintroduction of gluten.

While the familial incidence of coeliac disease is incontestable, some workers emphasise the importance of inheritance (Anderson *et al.*, 1972; McNeish and Anderson, 1974), and others the environment (Hoffman *et al.*, 1966; Walker-Smith, 1973). We here report coeliac disease with identical age of onset in a pair of monozygotic twins. This is the only well documented report of concordant monozygotic twins with genetic study, apart from that of David and Ajdukiewicz (1975) which included one set of adult female twins who were 'probably monozygotic'.

Case reports

White twin boys were born at term, without complications, and with a single placenta. Twin 1 weighed 2·6

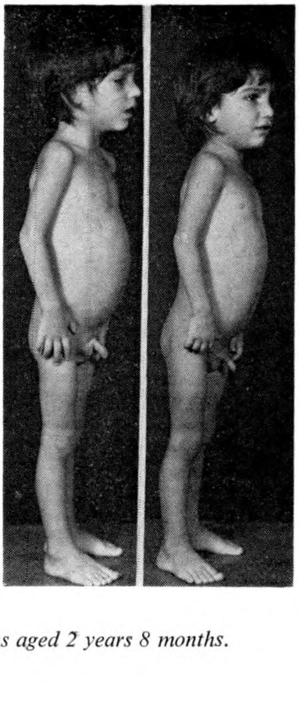
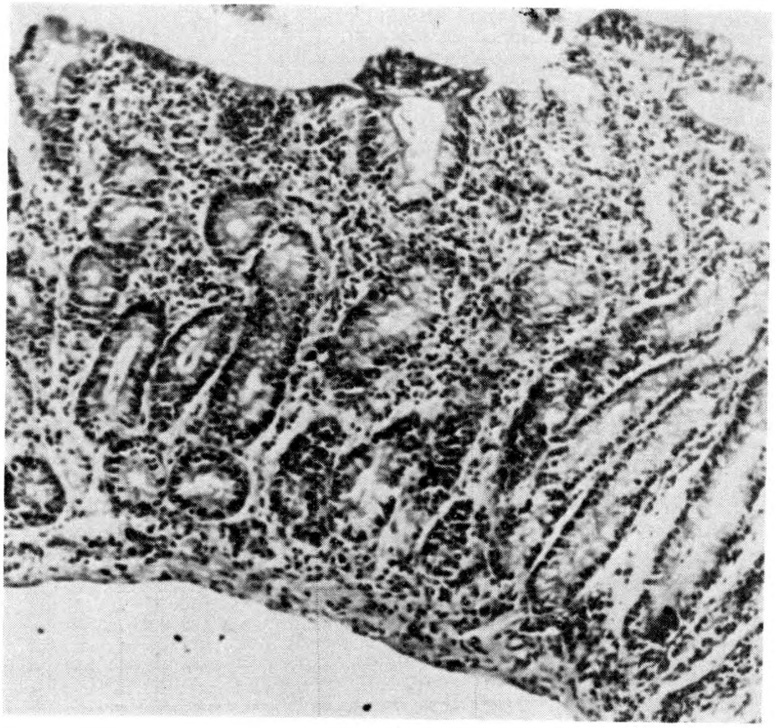
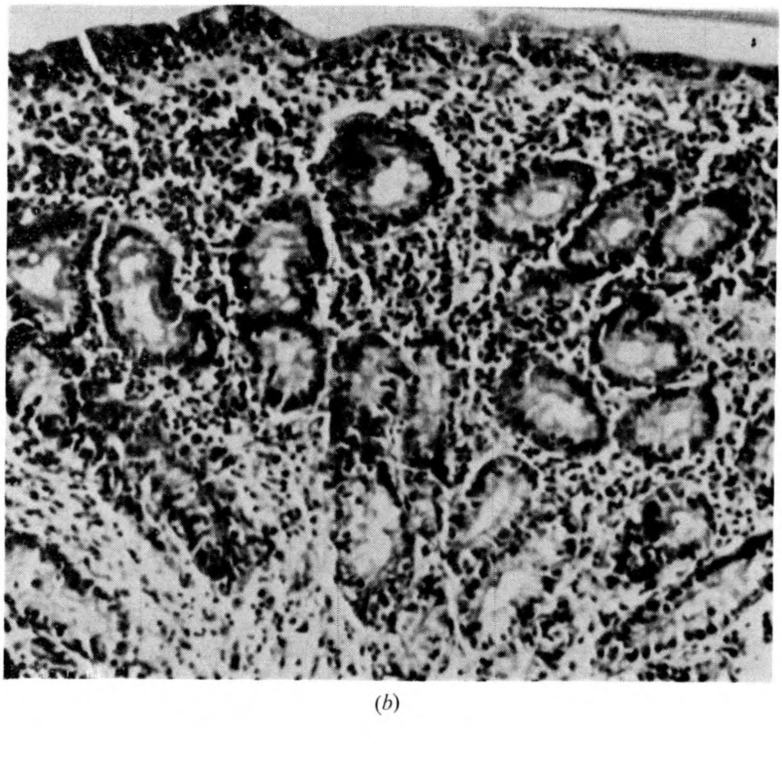


Fig. 1 *Twins aged 2 years 8 months.*



(*a*)



(*b*)

Fig. 2a, b *Jejunal histology of the twins.*

kg, twin 2 2·5 kg. Cows' milk was given from birth, and gluten-containing foods introduced at 4 months. They grew well until age 6 months, when both started to have episodes of diarrhoea with poor weight gains. At age of presentation, 2 years and 7 months, the stools were voluminous, yellowish, and shiny, were passed three times daily, and contained undigested food particles. Twin 1 then weighed 10·5 kg, length 88 cm; twin 2 weighed 10·4 kg, length 87 cm. Each was thin with protruding abdomen and wasted buttocks (Fig. 1). Small intestine biopsy was performed at the level of the duodenojejunal flexure, and in each was a typical mucosal pattern with absence of villi, cuboidal surface epithelium, hypertrophied crypts, and infiltration of the lamina propria by lymphocytes and plasma cells (Fig. 2).

Faecal fat excretion measured over a period of 72 hours gave 12·3 g/24h (43·3 mmol/24h) for twin 1 and 7·4 g/24h (26 mmol/24h) for twin 2.

Blood xylose after a loading dose (Roe and Rice, 1948) gave the following results: twin 1, 1st hour 26·2 mg/100 ml (1·7 mmol/l); 2nd hour 24·6 mg/100 ml (1·6 mmol/l). Twin 2, 1st hour 29·2 mg/100 ml (1·9 mmol/l); 2nd hour 24·6 mg/100 ml (1·6 mmol/l) (normal : 40 mg/100 ml ± 11).

MZ twin pregnancy was established by the following: (1) pregnancy with single placenta; (2) physical similarity of twins (Fig. 1); (3) dermatoglyphs. Unilateral comparison of the dermatoglyphic patterns of the left and right sides of the twins showed that the right hand of one twin was more like the right hand of the other, than was his own left hand. The total ridge count showed a difference of 8 between them. Holt (1961) reported that about 80% of MZ twins had differences of less than 20 ridges by total count, whereas only 30% of dizygotic twins had such small differences. (4) Blood groups. Both twins were A, D +, E −, $\bar{e}$ −, $\bar{c}$ +, C −, M +, N +.

Both parents and 2 brothers and 2 sisters were clinically normal, but it was not possible to carry out more extensive studies.

Both twins quickly responded to a gluten-free diet. After about 6 weeks the mother reintroduced a normal (gluten-containing diet) which was followed by severe clinical relapse. Since the reintroduction of a gluten-free diet, steady progress has been maintained to their present age (5 years). It was not possible to repeat the original biopsies.

Discussion

Monozygosity in the twins was based on the presence of a single placenta, similarity in physical appearance, and dermatoglyphic and blood group studies.

There are two reports in which only one of MZ twins was affected by the disease, indicating the possible involvement of environmental factors (Hoffman *et al.*, 1966; Walker-Smith, 1973). This occurred in one adult and one child pair respectively. McCrae (1969) suggested that a familial incidence, which may be as high as 44%, is evidence for the genetic basis of coeliac disease and he also emphasised the importance of environmental factors in the pathogenesis of the disease. David and Ajdukiewicz (1975), studying the familial incidence of coeliac disease, encountered 13 (9%) of 141 patients with a family history, and concluded that the disease could be transmitted by an incompletely penetrant autosomal dominant gene. The female preponderance noted in adult coeliacs was not evident in childhood coeliacs, with or without familial involvement.

We thank Professor Navantino Alves Filho for analyses of dermatoglyphs, Professor Marcos Borato Vianna for blood group determinations, and Dr Margot Shiner and Mr David Kingston for help with this paper.

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Recurrent attack of rotavirus gastroenteritis after adenovirus-induced diarrhoea

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SUMMARY A 14-month-old baby boy suffered a second attack of rotavirus gastroenteritis within one month of the initial one. The second attack followed a diarrhoeal episode associated with adenovirus. Gastrointestinal symptoms in the second attack were more severe than those of the first. The adenovirus-associated enteritis was mild compared with the illness in both episodes of rotavirus infection.

We report an infant in whom a second attack of rotavirus gastroenteritis occurred within a month. The second attack followed a diarrhoeal episode associated with type 7 adenovirus.

Case report

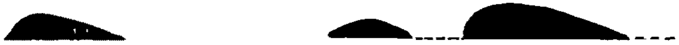
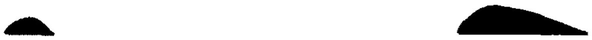
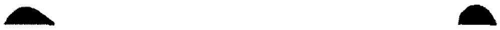
A 14-month-old baby boy was admitted on 8 February 1977 with typical acute gastroenteritis with diarrhoea, vomiting, anorexia, fever, and dehydration (Table). He received intravenous infusion and dietary treatment, and was discharged when completely recovered on 16 February. On 25 February he was brought to the outpatient clinic with a recurrence of diarrhoea. He had no vomiting or fever at that time and initially his condition improved but he continued to have loose stools. On 4 March he was readmitted with severe watery diarrhoea, frequent vomiting, and fever. Symptoms were more severe than those during the first admission; vomiting lasted for 5 days and diarrhoea for over a week. He was discharged when completely recovered on 19 March.

Laboratory data.

Electron microscopical examination

Stool specimens were consecutively collected and stored at − 70°C. The specimens were prepared for electron microscopy (EM) using the method of Flewett *et al.* (1974). Numerous rotavirus particles were found in the first and fourth stool specimens which were collected on 8 February and 4 March, but not in the other specimens. In the third specimen, collected on 25 February, a large quantity of adenovirus particles were found but no rotavirus ones. EM examination of the original specimens was

Table *Clinical and laboratory data on 3 episodes of diarrhoea in a 14-month-old infant*

	February					*March*				
	Admission		*Discharge*			*Admission*				*Discharge*
	8	*10*	*16*	*20*	*25*	*4*	*7*	*12*	*17*	*19*
Diarrhoea										
Vomiting										
Fever										
Virus in the faeces										
Rotavirus	++		—*		—*	++			—	
Adenovirus	—		—		++	—			—	
CF antibody titre to										
Rotavirus	<4				8			32	64	
Adenovirus type 3	<4				<4			<4	8	
Adenovirus isolated	<4				<4			8	16	
Neutralising antibody titre to adenovirus isolated	<2				<2			16	ND	

*Rotavirus particles could not be detected by immune electron microscopical examinations.
ND = not done.

repeated with the same results. Bearing in mind the possibility that a small number of rotavirus particles might be present but not detectable, we also performed immune electron microscopical (IEM) examinations of the second and third specimens: the results were negative.

Culture

All fresh stool specimens were cultured for bacterial pathogens with negative results. Virus isolation was attempted using primary human embryonic kidney (HEK) cells. A cytopathic agent was recovered from the third stool specimen collected on 25 February. The cytopathic effect was typical of adenovirus, and EM observation of the culture fluid identified the isolate as adenovirus. The isolate was grown in HeLa cells and was identified as type 7 adenovirus.

Serology

Complement-fixing (CF) antibody titre was measured simultaneously against rotavirus and adenovirus antigens. The human rotavirus antigen was prepared by the method of Bishop *et al.* (1974) from the virus-rich stools of patients with acute gastroenteritis. Two adenovirus antigens were used; one was prepared from the isolated adenovirus strain and the other from commercially obtained type 3 antigen. CF antibody to rotavirus converted to positive after the first attack and further increased in titre until the last attack of gastroenteritis. Seroconversion to adenovirus antigens was also found during the second and last episodes of diarrhoea, with somewhat higher titres against the isolated virus. Neutralising antibody to the adenovirus isolate was also found to develop concurrently (see Table).

Discussion

This case may provide valuable information about viral gastroenteritis in view of the reinfection with rotavirus and the apparent pathogenic role of adenovirus in acute diarrhoea.

Although it has been assumed that reinfection with rotavirus could occur with second and subsequent episodes of gastroenteritis or in subclinical form, we are aware of only one patient who had a second episode of rotavirus enteritis (Davidson *et al.*, 1975). That patient, admitted with acute enteritis at 6 and again at 14 months of age, showed rotavirus particles in stools on both occasions. The interval between the attacks of rotavirus-induced gastroenteritis was shorter in our patient. As it is probable that $<10^5$ virus particules per ml would not be detected by routine EM examination, the technique of IEM was used to look for rotavirus during the intervening period. Even with the negative results of IEM, the possibility of an endogeneous reinfection still remained. In that case, adenovirus infection in the intestinal tract might have acted as a trigger for the second invasion of rotavirus. Recent studies have given evidence suggesting the existence of different serotypes among human rotavirus strains (Thouless *et al.*, 1978; Zissis and Lambert, 1978), so it may be possible for the same person to experience reinfection with a different antigenic strain of rotavirus. We could not examine the antigenic variation of rotaviruses recovered from the episodes of gastroenteritis, but it was interesting that gastrointestinal symptoms in the last episode were more severe than those of the first in spite of the pre-existing antibody.

In stools, apart from rotavirus, the second most common group of viruses easily recognisable by EM are adenoviruses (Bruce White and Stancliffe, 1975; Bryden *et al.*, 1975). We have observed adenoviruses in about 5% of all cases of gastroenteritis occurring in the winter (Kogasaka *et al.*, 1975). An aetiological role of such adenoviruses in gastroenteritis has long been controversial because of the lack of epidemiological evidence. The difficulty of growing in cell culture some adenoviruses which are visible by EM in great numbers contrasts with the easy propagation of some strains of adenoviruses undetectable by EM (Bryden *et al.*, 1975; Madeley *et al.*, 1977). We have used various cell cultures trying to grow adenoviruses visible by EM, and lately found HEK to be the only susceptible cells available in our laboratory. So far, we have grown 5 strains from 7 stool specimens found to be positive by EM, after a few blind passages in HEK (unpublished). One of those strains was recovered from the present patient and it enabled us to test for CF and neutralising antibody responses against the homologous strain. The results showed that primary infection with this type 7 adenovirus was present in the patient. The adenovirus was not just a passenger virus.

The adenovirus-associated enteritis in this case was remarkably mild compared with the illness in both episodes of rotavirus infection. Diarrhoea lasted only a few days and was not accompanied by vomiting. Flewett *et al.* (1975) reported an outbreak of adenovirus-associated diarrhoea in a long-stay children's ward. They mentioned the mildness of this type of enteritis in comparison with rotavirus enteritis experienced in the same ward. Thus acute enteritis associated with adenoviruses seems to be generally mild. Fatal adenovirus gastroenteritis described by Whitelaw *et al.* (1977) might be exceptional.

The present case emphasises the need to look for a different pathogen in repeated episodes of gastroenteritis.

Addendum

Since this paper was submitted recurrent gastroenteritis associated with different rotavirus serotypes has been reported by Fonteyne *et al.* (1978) and Rodriguez *et al.* (1978).

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Pathogenesis of oxytocin-induced neonatal hyperbilirubinaemia

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SUMMARY 100 term (gestation at least 37 weeks), vertex presenting, vaginally delivered, and fetomaternal blood-group-compatible neonates were studied to evaluate the pathogenesis of neonatal hyperbilirubinaemia induced by oxytocin. 50 infants were born after oxytocin infusion for augmentation of labour and the other 50 were delivered spontaneously. The babies born after oxytocin induction of labour attained significantly higher serum bilirubin levels at age 72 ± 12 hours than the controls. Infants born after oxytocin showed significant hyponatraemia, hypo-osmolality, and enhanced osmotic fragility of erythrocytes at birth. These biochemical and physiological alterations can be explained by the antidiuretic effects of oxytocin and concomitant administration of large quantities of electrolyte-free dextrose solutions used to administer it. Our observations suggest that cord serum sodium and/or osmolality should be estimated and infants with serum sodium <125 mmol/l and/or osmolality <260 mmol/kg should be considered for prophylactic administration of phenobarbitone.

The role of oxytocin in causing neonatal hyperbilirubinaemia is now generally accepted (Oski, 1975; Chew and Swann, 1977). However, the pathogenesis of such a hyperbilirubinaemia is still a matter of speculation. A relatively immature glucuronyl transferase system due to absence of the hormonal upsurge of normal labour (Sims and Neligan, 1975) and an enhanced placento-fetal transfusion due to oxytocin-induced uterine contractions, with resultant increase in red cell mass in neonates (Oski, 1975), have been suggested. To explain the pathogenesis of oxytocin-induced neonatal hyperbilirubinaemia, we tested the antidiuretic effect of oxytocin.

Subjects and methods

From September to November 1977, 100 term (gestation at least 37 weeks), vertex presenting, vaginally delivered, fetomaternal blood-group-compatible neonates born at this hospital were studied. 50 of them were born after oxytocin infusion for induction or augmentation of labour (group 1), while the other 50 were delivered spontaneously (group 2). Oxytocin infusion in 5% dextrose was started at a rate of 2 mU/min (infusate oxytocin concentration of 4 U/l), increasing by 2 mU/min every half-hour, until effective uterine contractions were achieved. The duration of oxytocin administration varied between 4 and 24 hours. Serum bilirubin (Michaelsson's modification of Jendrassik-Grof-Nosseline method), serum sodium (by flame photometer), and serum osmolality (by Fiske osmometer), were estimated in the cord blood samples of all the infants. Serum bilirubin and sodium estimation was again done at postnatal age of 72 ± 12 hours. Saline osmotic fragility of cord blood erythrocytes was determined in 30 infants from each group. These infants did not differ significantly from the others. Phototherapy was withheld until the sample on day 3 was collected. None of the babies who developed early jaundice (<24 hours) or hyperbilirubinaemia (serum bilirubin >200 μmol/l; >11·7 mg/100 ml) had cephalhaematoma, G-6-PD deficiency, or an intrauterine infection. Statistical significance of differences in serum bilirubin, sodium, osmolality, and red cell osmotic fragility in the two groups was determined by Student's *t* test. The correlation coefficient was calculated between serum sodium and serum osmolality at birth, and serum bilirubin at 72 ± 12 hours of age.

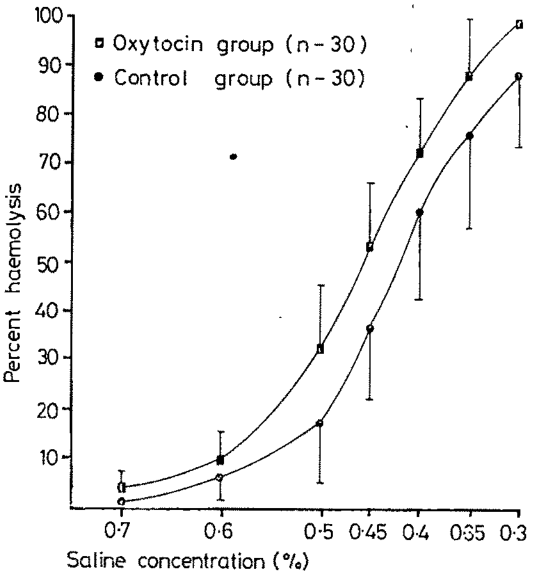

Fig. 1 *Significantly increased osmotic fragility of cord blood erythrocytes in neonates born after oxytocin infusion during labour is compared with control group. Bars show standard deviation.*

Results

Both groups were comparable as regards distribution of birthweights (2·83 ± SD 0·34 and 2·79 ± SD 0·41 kg respectively), gestational age (38·7 ± SD 1·8 and 39 ± SD 1·5 weeks respectively), asphyxia neonatorum, and maternal pre-eclamptic toxaemia. Cord serum sodium level was 131·3 ± SD 7·0 mmol/l and osmolality 273·4 ± 16·6 mmol/kg in group 1. These values were significantly higher in group 2—namely, cord serum sodium level 137·4 ± SD 5·3 mmol/l and osmolality 288·0 ± SD 8·4 mmol/kg (P<0·01 to <0·001). Haemolysis started at a higher saline concentration and was completed earlier in group 1 (Fig. 1). Serum bilirubin at birth was 30 ± 10 μmol/l (1·73 ± SD 0·6 mg/100 ml) in group 1, and 29 ± 9 μmol/l (1·69 ± SD 0·5 mg/100 ml) in group 2. At age 72 ± 12 hours, babies in group 1 attained significantly higher mean serum bilirubin levels of 166 ± 51 μmol/l (9·7 ± SD 3·0 mg/100 ml) compared with 113 ± SD 44 μmol/l (6·6 ± 2·6 mg/100 ml) in group 2.

A significantly negative correlation was found between cord serum sodium and osmolality, and serum bilirubin at 72 ± 12 hours of age (Fig. 2). Babies with cord serum sodium level up to 125

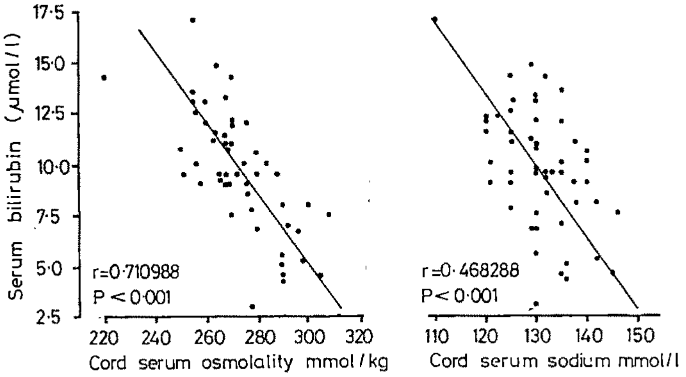

Fig. 2 *Negative correlation between cord serum osmolality and sodium, and serum bilirubin level at postnatal age 72 ± 12 hours.*

mmol/l had a mean serum bilirubin level of 195 ± SD 41 μmol/l (11·4 ± SD 2·4 mg/100 ml). Those with cord serum sodium levels between 126 and 135 mmol/l, and above 135 mmol/l had a mean serum bilirubin level of 163 ± SD 53 μmol/l (9·53 ± SD 3·08 mg/100 ml) and 131 ± SD 41 μmol/l (7·66 ± SD 2·41 mg/100 ml) respectively. The difference is statistically significant ($P<0·01$).

The hyponatraemia observed at birth in group 1 had disappeared by 72± 12 hours, when serum sodium levels were identical in the two groups (136·53 ± SD 6·07 mmol/l in group 1 and 138·12 ± SD 4·58 mmol/l in group 2).

Discussion

The findings in this study show that oxytocin infusion during labour results in transplacental hyponatraemia and hypo-osmolality, increased osmotic fragility of cord blood erythrocytes, and a higher bilirubin level at postnatal age 72 ± 12 hours. The negative correlation between cord serum sodium and osmolality, and serum bilirubin at age 72 ± 12 hours, strengthens our previous observation that transplacental hyponatraemia and hypo-osmolality play a significant role in the pathogenesis of oxytocin-induced hyperbilirubinaemia (Singhi and Singh, 1977). It is well known that when administrated by continuous IV infusion, oxytocin by virtue of its antidiuretic effect results in expansion of maternal extracellular fluid (ECF) with dilutional hyponatraemia and hypo-osmolality (Abdul-Karim and Assali, 1961; Morgan *et al.*, 1977; Schwartz and Jones, 1978). Large amounts of electrolyte-free solution—namely 5% dextrose used as a vehicle for oxytocin infusion—further aggravate these changes. Since maternal and fetal body fluids are in constant transplacental equilibrium, an expansion of fetal ECF, with resultant neonatal hyponatraemia and hypo-osmolality follows (Battaglia *et al.*, 1960; Schwartz and Jones, 1978). When blood is rendered hypo-osmolal, there is an inflow of water into erythrocytes (Blum and Forster, 1970). As a result erythrocytes swell and become osmotically more fragile. Significantly enhanced osmotic fragility of cord blood erythrocytes in the present study supports this hypothesis. These swollen and hyperfragile erythrocytes are easily trapped by the spleen, resulting in net higher bilirubin.

Our observations suggest that caution should be exercised while using oxytocin for induction or augmentation of labour, especially when additional risk factors for hyperbilirubinaemia coexist. If oxytocin administration is unavoidable, maternal serum sodium and osmolality should be maintained within the normal range by using dextrose saline as a vehicle for oxytocin instead of plain dextrose solution. Cord serum sodium and, if possible, osmolality should be estimated in all babies born after oxytocin-induced or augmented labour. Infants with cord serum sodium level < 125 mmol/l and/or osmolality of < 260 mmol/kg are at risk of developing hyperbilirubinaemia and should be considered for prophylactic administration of phenobarbitone as an inducer of the hepatic microsomal enzyme system.

We thank Professor O. P. Ghai, Department of Paediatrics, All-India Institute of Medical Sciences, New Delhi for his encouragement and advice.

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Correspondence

Early use of sodium nitroprusside in respiratory distress syndrome

Sir,

The management of respiratory distress syndrome (RDS) with continuous positive airways pressure and intermittent positive pressure ventilation (IPPV) is well established. Sometimes these measures are insufficient to maintain adequate oxygenation. A report from Liverpool (Abbott *et al.*, 1978) described the comparatively late use of sodium nitroprusside in a baby with RDS. We describe the early use of sodium nitroprusside in a baby with severe RDS.

A baby boy, son of a 21-year-old Kenyan-Asian, was born at 28 weeks' gestation and weighed 1·1 kg. His mother had been admitted 8 days before delivery with spontaneous rupture of membranes. 24 hours before delivery she had become pyrexial and been treated with cephradine. Dexamethasone and ritodrine were given during labour, and delivery was assisted by Wrigley's forceps. The baby needed IPPV for 15 minutes after birth and rapidly developed severe RDS which required ventilation within 2 hours of delivery. Pa_{O_2} was initially maintained at 10 kPa (75 mmHg), but at 6 hours it had fallen and could not be maintained above 4 kPa (30 mmHg). At this stage the ventilator settings were: ratio inspired:expired (I:E) 4:1, pressures I:E 25/5 cm H_2O, F_{IO_2} 0·9, ventilator rate 40/min.

Sodium bicarbonate infusion (2 mmol/kg per 24 hours) was begun at 4 hours, and sodium nitroprusside (120 μg/

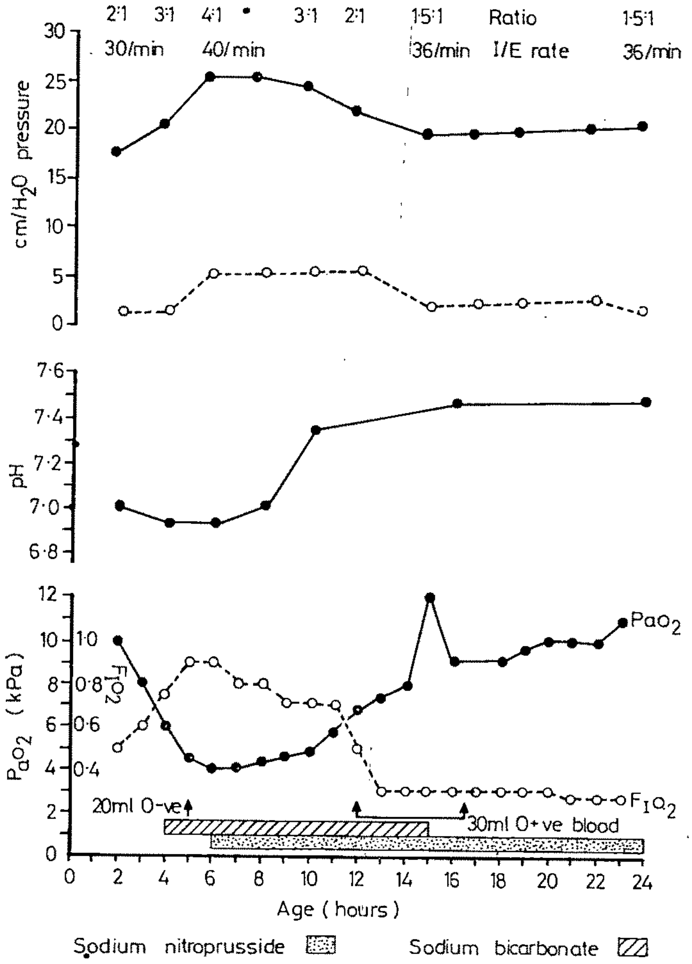

Figure *The early use of sodium nitroprusside in respiratory distress syndrome.*

kg per hour) at 6 hours. Fresh donor blood, total 50 ml, was transfused to maintain the systolic blood pressure above 50 mmHg. At 8 hours the baby's condition began to improve with an increase in Pao_2, and at 15 hours, Pao_2 could be maintained at 12 kPa (90 mmHg) with the following ventilator settings: ratio I:E 1·5:1, pressures I:E 18/2 cm H_2O, Fio_2 0·3, ventilator rate 36/min.

The sodium nitroprusside infusion was continued for 24 hours after which time the dose was logarithmically reduced every 12 hours until it was finally stopped at 72 hours. During the next 12 hours the blood pressure rose from 50/40 to 90/60 mmHg but it returned to normal 24 hours after discontinuing the infusion. The infant's progress in the first 24 hours of life is shown in the Figure.

The baby continued his difficult neonatal period with a respiratory tract infection on day 5 and a Gram-negative septicaemia on day 14. He was discharged home on day 56 and to date, at 3 months, shows normal development.

In RDS there is often very pronounced right-to-left shunting (Strang, 1966). Sodium nitroprusside is a direct-acting vasodilator (Tinker and Michenfelder, 1976) and its action on the pulmonary vascular bed reduces pulmonary vascular resistance, thereby increasing pulmonary blood flow. This decreases right-to-left shunting and results in an increased Pao_2.

Compared with the case in Liverpool, we gave sodium nitroprusside at a very early stage in the illness. The fact that this was followed by such a rapid improvement is convincing evidence of its therapeutic value. Thus sodium nitroprusside infusion may have an important role in the management of babies with severe RDS who deteriorate in spite of mechanical ventilation.

Attention has recently been drawn to the possible toxic effects of sodium nitroprusside (*British Medical Journal*, 1978). Our observation that 50 ml blood (about 57% of blood volume) was needed to maintain systolic blood pressure indicates that sodium nitroprusside should be used only if there are adequate facilities for biochemical and blood pressure monitoring.

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Weaning very low birthweight infants from mechanical ventilation using intermittent mandatory ventilation and theophylline

Sir,

We read with interest the paper by Barr (*Archives*, 1978, **53**, 598), and should like to report our recent experience with aminophylline in two very low birthweight infants.

Case 1

This infant born at a gestational age of 30 weeks weighing 1190 g was severely asphyxiated at birth and required mechanical ventilation for the first 4 days of life. At age 4 weeks, 48 hours after the introduction of nasojejunal feeds, he developed necrotising enterocolitis and required a 40 cm small bowel resection. At the same time, mechanical ventilation was recommended because of recurrent apnoea and bradycardia: initial ventilator settings were: peak pressure 25 cm H_2O, positive end expiratory pressure 5 cm H_2O, and frequency 28 cycles/min.

During the next 6 days attempts to wean him from the ventilator by decreasing the rate to 16 cycles/min resulted in episodes of bradycardia and cyanosis with the capillary Pco_2 increasing from 4·7 to 7·9 kPa (35 to 59 mmHg). In view of this, aminophylline was administered with a loading dose of 3·3 mg/kg intravenously followed by a maintenance dose of 3 mg/kg per day in three divided doses. Serum aminophylline level 48 hours after starting treatment was 8 mg/l (therapeutic range 6·6–11 mg/l. 11 mg/l, Shannon *et al.*, 1975).

24 hours after the introduction of aminophylline, capillary Pco_2 had fallen to 5·3 kPa (40 mmHg); there had been no change in the ventilator settings. The infant was then successfully weaned from the ventilator.

Case 2

This infant was also born at 30 weeks' gestation and weighed 1150 g. At age 12 days he began to have episodes of apnoea and bradycardia. Capillary blood-gases at this stage showed a Pco_2 of 8·9 kPa (67 mmHg). Biochemical and infective causes for the apnoea were excluded while the chest *x*-ray was compatible with early chronic lung disease of prematurity. A loading dose of 3·8 mg/kg aminophylline was given intravenously followed by a maintenance dose of 3·1 mg/kg per day in three divided doses. Serum aminophylline level 48 hours after starting treatment was 6·5 mg/l. 24 hours after the loading dose of aminophylline, the capillary Pco_2 had fallen to 6·3 kPa (47 mmHg) with no recurrence of the apnoea.

Our results support Barr's observations that aminophylline may be an aid in the weaning of infants from mechanical ventilation and, like caffeine (Aranda *et al.*, 1977), will reduce the Pco_2, probably by increasing the ventilatory effort and thereby increasing alveolar ventilation.

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Bilateral Wilms's tumour in Klippel-Trenaunay syndrome

Sir,

Involvement of the viscera, including the kidneys, is not uncommon in the Klippel-Trenaunay syndrome (KTS) (haemangiectatic hypertrophy) but the occurrence of Wilms's tumour in KTS has not been described, although one child with bilateral nephroblastomatosis and KTS is known (Mankad *et al.*, 1974). We have recently observed an infant with KTS and bilateral Wilms's tumour.

The child presented from birth with typical signs of KTS (unilateral hypertrophy of the left ear, tonsil, labium majus, and lower extremity—especially the third toe—cutaneous haemangiomas on the trunk, subcutaneous haemangioma on the left thigh, hyperpigmentation at the right neck and arm). Psychomotor development was normal. At age one year, a left abdominal mass was found on routine examination. IVP showed an enlarged left kidney with distortion of the calyces. At laparatomy a nodular tumour originating from the left kidney was found and a nephrectomy performed. The right kidney showed small nodules which were biopsied. There was no evidence of metastasis at operation or in subsequent *x*-rays. The resected kidney measured 16 × 10 × 11 cm. The renal parenchyma was reduced to 8 mm thickness surrounding the tumour mass. Histologically glomerular and tubular differentiation and solid blastomatous structures were evident, consistent with Wilms's tumour. The biopsy of the right kidney showed similar lesions. Chemotherapy and radiation therapy were given. 12 months after nephrectomy the patient remains well.

Wilms's tumour has been reported in association with congenital hemihypertrophy, in the Beckwith-Wiedemann syndrome, and in association with aniridia.

Although a common embryological basis for KTS and Wilms's tumour is not yet established, the association may be more than chance.

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Neonatal effects of maternal clomipramine therapy

Sir,

We read with interest the study by Crome and Braithwaite (*Archives*, 1978, **53**, 902). We encountered a similar problem recently in a neonate affected by maternal clomipramine (Anafranil) in which the main problems were instability of body temperature and jitterness.

The mother has been taking clomipramine, 25 mg three times a day for 18 months for depression, and this treatment continued unchanged throughout her normal pregnancy. The baby boy born at term had a birthweight of 3·14 kg, and a normal Apgar score, but at 12 hours he became dusky during feeding and had a rectal temperature of 35·4°C. His tendency to hypothermia was aggravated by feeding and handling, and persisted for 4 days. No biochemical or infective cause was found for this or for subsequent problems.

He became jittery on the 2nd day of life and this continued for 48 hours; perhaps this was the effect of drug withdrawal. Treatment with phenobarbitone (10 mg/kg per day) controlled this problem and may have induced the hepatic conjugating enzymes needed to metabolise clomipramine.

Plasma clomipramine levels in the baby were <20 μg/l on the 1st and 3rd days of life, but the corresponding levels of its active metabolite, chlordesipramine, were higher at 116 and 96 μg/l.

The baby made an uneventful recovery and was making normal developmental progress at ages 3 and 6 months.

The use of tricyclic antidepressant drugs in pregnancy has been linked with the birth of malformed infants (Barson, 1972; Idänpään-Heikkilä and Saxén, 1973), but little is recorded about the associated neonatal morbidity. Hypothermia has been noted as a side effect of clomipramine treatment in adults, but this was not found by Crome and Braithwaite in their review of tricyclic drug poisoning in older children.

The frequency of the use of antidepressant drugs in pregnancy is unknown, but they should be avoided if possible.

We acknowledge the help of the National Poisons Information service at New Cross Hospital, Poisons Unit, London, which carried out the estimation of plasma drug concentrations.

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Evaluation of the Sheffield system for identifying children at risk from unexpected death in infancy

Sir,

The conclusions drawn by Oakley *et al.* (*Archives*, 1978, **53**, 649) are so at variance with the data they present that we must comment. Briefly, the re-analysis below shows that the birth data from Birmingham and Newcastle are remarkably similar and are consistent with the two sets of Sheffield birth data (Protestos *et al.*, 1973; Carpenter *et al.*, 1977). Also the hypothesis that the birth scoring system (Carpenter *et al.*, 1977) would be equally effective in Birmingham, Newcastle, and Sheffield is not rejected ($P = 0\cdot14$). Furthermore, although our birth scoring system performed relatively poorly on the Birmingham data compared with Sheffield, its level of performance there is the same as that of the scoring system studied by Alberman and Goldstein (1970) when it was shown that maximum benefit is gained by the differential allocation of resources to a high-risk group.

Table 3 of Oakley *et al.* (1978) appears to show that the birth data from Birmingham differ from those collected in Newcastle, and the text indicates that this is how the authors view their data. Their mistake arises from the method of analysis. For example, invasive investigations in pregnancy are reported as significantly associated with the Birmingham cases but not with Newcastle ones. What is not apparent is that the difference between Birmingham cases and controls is smaller than the difference between cases and controls in Newcastle in this respect, as shown in Table C1.

Table C1 *Percentage differences between cases of unexpected death and live controls in Birmingham and Newcastle*

Variable	*City*	*Cases (%)*	*Controls (%)*	*Percentage difference*
Invasive investigations during pregnancy	Birmingham	32·5	26·5	6·0
	Newcastle	19·6	12·5	7·1
Sex	Birmingham	51·8	57·8	−6·0
	Newcastle	69·6	46·4	23·2

Re-analysis of risks associated with factors. The question then arises, Is there any evidence that their data from Birmingham and Newcastle differ in regard to the risks of unexpected death associated with the 18 factors they list? There are several approximate statistical methods for examining this question. We have used the exact method of Zelen (1971) and have applied it to the data presented in Table 3 of the paper by Oakley *et al.* The only significant difference ($P = 0\cdot025$) between the two sets of data is that relating to sex, Table C1. This is mainly because the proportion of male cases in Birmingham is unusually low (51·8%) while that in Newcastle is exceptionally high (69·6%) (Carpenter, 1972). At least one P value as small as this may occur by chance in 18 significance tests.

The overall impression is that the two data sets are remarkably similar. The average P value for the 18 tests of homogeneity is 0·72 which is substantially larger than the expected value of 0·5. If the 18 comparisons are regarded as independent, the two sets of data appear significantly similar ($P<0\cdot00003$), but the variables are all interrelated which probably accounts for the unexpected similarity. For 5 factors: birthweight, twin birth, urinary tract infection during pregnancy, gestation <37 weeks, and admission to special care baby unit, the relative risks cannot be more similar, given the number of infants with the factor in each set of data.

Having found that the data from Birmingham and Newcastle are essentially similar, are they compatible with the findings of the two surveys of birth data in Sheffield reported by Protestos *et al.* (1973) and Carpenter *et al.* (1977)? Our analysis is confined to 7 of the 8 factors in the birth scoring system described by Carpenter *et al.* (1977). We cannot include the 2nd stage of labour because the data are grouped differently. For each factor, we tested whether the 4 estimates of relative risk, derived from the 4 data sets, could be regarded as homogeneous. In no case was the hypothesis of homogeneity rejected. The smallest P value was 0·085 for mother's blood group. This is hardly surprising because the two Sheffield data sets are significantly different in respect of mother's blood group (Carpenter *et al.*, 1977). Combining the 7 significance tests also provided no suggestion of heterogeneity.

Consequently the best information available is provided by combining all the data. The results of doing so are presented in Table C2 which shows that the differences are significant for each of the 7 variables. Differences are similar to those previously reported by Carpenter *et al.* (1977).

Table C2 *Combined birth data from Birmingham, Newcastle, and two Sheffield surveys.* (*334 cases of unexpected infant death and 389 live controls*)

	Cases (%)	*Controls (%)*	*Percentage difference**	*P*
Mother's age <24	60·8	43·8	17·0	0·000008
Birthweight <3000 g	45·3	27·1	18·2	0·0000006
Intention to breast feed	20·5	31·4	−10·9	0·0014
Primiparous	22·7	37·0	−14·3	0·00005
Twins	5·7	0·5	5·2	0·00009
Urinary tract infection	12·4	7·3	5·1	0·0375
Blood group A	35·4	46·3	−10·9	0·0041

*Combining the four data sets by Cochran's test (Armitage, 1971) gives mean % differences which are up to 1·2% smaller and which are slightly less significant. But exact tests (Zelen, 1971) of the combined relative risks are more significant than shown.

Birth scoring. Using stepwise discriminant analysis, Oakley *et al.* (1978) obtained discriminant functions for Birmingham and Newcastle which had only 3 variables in common, only one of which was included in our birth scoring system—i.e. mother's age. The reader is left with the impression of a mass of heterogeneous data. Stepwise analyses are very arbitrary in their selection of variables and heterogeneity can be established only by formulating and testing the appropriate hypothesis. Oakley *et al.* give no hint that this has been done, nor have they tested whether their data conflict with our scoring system. All their analysis shows is that if we had started with one of their sets of data we might be using a scoring system which superficially would look very different from our present one.

Oakley *et al.* report the results of applying our second scoring system to their data. Testing the hypothesis that infants with scores >500 are at the same risk in Birmingham and Newcastle we find P = 0·13. When we compare their results with our evaluation (Table 9 of Carpenter *et al.*, 1977) we again find no significant differences (P = 0·14). Taking all these data together, 54% of cases had scores >500 compared with 30% of controls. It is now clear that the choice of 500 as the critical score is too low if the high risk group is only to include about 16% of controls. Raising the critical score also reduces the proportion of cases in the high risk group. In any case there is no good reason for merely considering high and low risk groups as risk rises exponentially with score.

The principal criticism of Oakley *et al.* is that 'the degree of discrimination that the Sheffield "at birth" score achieved in either Birmingham or Newcastle during the study period is not one that would be of use in a prospective prevention programme, . . ." Sensitivity and specificity may be combined in the Youden index, J (Armitage, 1971) which is simply the difference between the percentage of cases and controls in the high risk group. For our prospective study, J = 38%; for the Newcastle data, J = 34%; for the Birmingham data, J = 13%. Alberman and Goldstein (1970) made a statistical evaluation of at-risk registers and showed that maximum benefit is gained by the differential allocation of resources to a high risk group. The value of J for the risk register they discussed is 13%, which is identical with that observed in Birmingham.

We have never said that the scoring system developed for identifying high-risk infants in Sheffield would work in other cities. The wide range of postperinatal mortality rates indicates that differences between cities are likely, but so far the reported differences may be attributed to random variation. We believe a scoring system along the lines we have described provides a practical method of improving the effectiveness of primary care.

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Drs Oakley and Stanton comment:

Our co-author Mrs J. Tavaré is now living in the USA, and we have had insufficient time to obtain her reply to the comments of Dr Carpenter and his colleagues on the statistical methods used in our paper.

There are always many ways of analysing a particular data set. Dr Carpenter and his colleagues are right in observing that our paper was primarily concerned with the *practical* application of the Sheffield scoring system to prospective prevention programmes, although we confirmed that the system discriminated at a statistically significant level between children who die, and the living control population.

A system which in Birmingham identified fewer than half the children who subsequently died while scoring one-third of the normal population at risk may be statistically valid, but we believe it has no place in primary care where we are dealing with the lives of infants and not statistics. Using the present system could well result in a positive maldistribution of primary care services by creating a false sense of security, and directing attention away from potentially vulnerable children who do not score at risk.

It is possible that future work in the Department of Health and Social Security's Multicentre Postneonatal Study will produce an effective at-risk system. Meanwhile, we are still of the opinion that scoring systems should only be used as research tools to indicate groups of infants that require particular study to investigate the aetiological factors of the sudden infant death syndrome.

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Archives of Disease in Childhood, 1979, **54**, 408

Book reviews

Paediatric Therapeutics. Edited by H. B. Valman. (Pp. 231; illustrated + tables. £7·75 paperback.) Blackwell: Oxford. 1979.

Any book devoted solely to treatment inevitably raises a doubt—is it really feasible to separate treatment from diagnosis, prognosis, and the rest? This principle apart, the rate of change of treatments tends to be rapid, new techniques and new drugs are being introduced all the time, old drugs and antibiotics are re-evaluated, given in different dosages, or become ineffective for various reasons, such as bacterial resistance. Hence I have hitherto looked with little favour on those massive and wordy volumes devoted to paediatric therapy which are almost as big as a complete textbook of paediatrics. Within a year or two they are already out of date and are to be seen growing dusty and unused on the shelves.

Coming to this book, my prejudices were disarmed by finding that both O. H. Wolff in his Foreword and the Editor in his Preface themselves frankly discuss the objections to books devoted solely to treatment, and they supply arguments to justify publication of this particular book. Firstly, we seem to be entering a new era where drugs can be used more rationally, based on expanding knowledge of their pharmokinetics and the increasing use of measurements of serum levels. So the first 3 of the book's 12 chapters are sensibly devoted to the fundamental aspects of the subject.

Secondly, the unpretentious format of the book, a paperback of 230 pages with a limited number of authors, has enabled rapid publication (I noted at least one 1978 reference) and will, it is to be expected, facilitate frequent new editions.

The remaining 9 chapters are devoted to epilepsy (B. D. Bower, to whom thanks for his forthright appraisal of phenobarbitone 'probably has little place . . .',) urinary infections (J. M. Smellie), nephrosis (T. M. Barratt), respiratory infections (H. Simpson), asthma (R. S. Jones), gastroenteritis (H. B. Valman), neonatal bacterial infection (P. M. Davies), leukaemia (T. M. McElwain), and diabetes (D. B. Grant). Judged by the criterion of whether an article provides something more than merely dealing with its subject in a way any standard textbook might do, I judged the majority did so, but there did seem very little new to say about the therapy of either gastroenteritis or diabetes.

One minor and possibly pedantic quibble, although drug dosage expressed as mg/kg/day is admittedly understood by everybody, this strictly does not mean mg. kg^{-1}. day^{-1} and would be better eliminated from a book designed to make clinical medicine more scientific.

In sum, an admirable book which should be the forerunner of many editions.

DOUGLAS GAIRDNER

Pulmonary Disease of the Fetus, Newborn, and Child. Edited by E. M. Scarpelli, P. A. M. Auld, and H. S. Goldman. (Pp. 680; illustrated + tables. £37·50 hardback.) Lea & Febiger: Philadelphia. 1978.

This is the companion volume to *Pulmonary Physiology of the Fetus, Newborn, and Child* (1975). There are no fewer than 23 contributors to the 19 chapters and the problems of multiple authorship have not been entirely overcome, stricter editing might have avoided some of the pitfalls and resulted in a smaller, less expensiv book.

The best chapters are those dealing wit intensive care; in particular, the one o airway management and cardiopulmonar resuscitation is a model of clarity an brevity. There are also 2 chapters devote to neonatal intensive care and the variou forms of respiratory distress in the newborn. Each contains some excellen practical guidelines although some of th advice given—for example, on the use an abuse of umbilical catheters—would b highly controversial in this country; fo some inexplicable reason these 2 chapter are irritatingly separated by one on th pathology of developmental anomalies o the lung. A section on thoracic surger includes quite a lot of surgical techniqu which, although not sufficiently detaile for surgeons, contains helpful hints fo paediatricians who are left 'holding th baby' postoperatively. The chapter o pulmonary radiology contains many clea *x*-rays illustrating the common and som very uncommon conditions; there ar also practical tips on how to interpre unusual *x*-ray appearances. The section on infections and chronic pulmonar disease are competent but unexceptional The remaining chapters deal with genera topics—such as, pathophysiology, inhalation therapy anaesthesia, sudde infant death, and extrapulmonary disease Each chapter is supplemented with usefu references.

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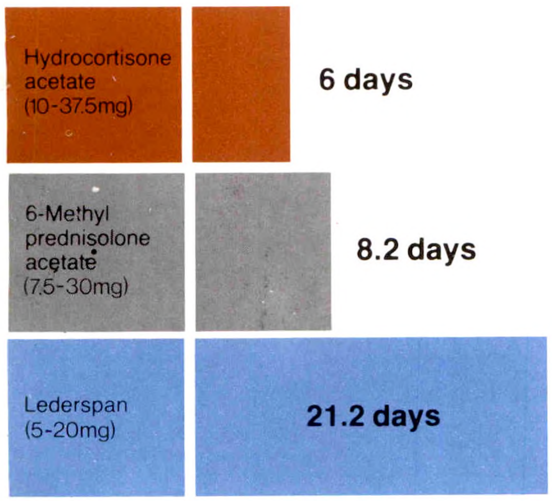
Comparison between Hydrocortisone acetate, 6-Methyl prednisolone acetate, and Lederspan.[2]



Comparative duration of pain relief.

Lederspan injections are needed less frequently than other injectable steroids.

Lederspan. Minimal diffusion outside the injected area.

The very low incidence of systemic reactions[3] suggests that there is minimal diffusion outside the injected area.

In a trial comparing methylprednisolone with Lederspan (dosage 20 mg) ..."No serious side effects were observed."[3]

Local reactions are rare.

> *"None of our cases showed atrophy of the skin or subcutaneous tissue at the site of injection ..."*[4]

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PRESCRIBING INFORMATION

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By intra-articular and intra-synovial injection Lederspan should be injected directly into the affected joint, or synovial space. Excessive synovial fluid may be removed be aspiration before administering Lederspan. In treating conditions such as tendinitis or tenosynovitis care should be taken that Lederspan is injected into the space between the tendon sheath and tendon and not into the tendon itself.

DOSAGE Adults and Children By intra-articular and intra-synovial injection: 2-30 mg (0.1-1.5 ml) depending on the size of the joint, the degree of inflammation and the amount of fluid present. In general, large joints (such as knee, hip, shoulder) require 10-30 mg, whereas small joints (such as interphalangeal, metacarpophalangeal) require 2-6 mg. Since Lederspan provides prolonged activity, injections into a single joint or synovial space more frequently than every 3-4 weeks are not recommended. Repeated intra-articular injections should be as infrequent as possible,consistent with adequate patient care.

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Archives of Diseases in Childhood, 1979, **54**, 409–414

Clinical events relating to intraventricular haemorrhage in the newborn

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SUMMARY Continuous measurements of arterial pressures, heart rates, respiratory movements, and respiratory rates were made from birth in 44 infants at risk from intraventricular haemorrhage (IVH). 17 babies died with IVH, in 10 of whom the event was timed objectively. Events in these babies were compared with survivors of similar birthweights, gestational ages, severity of birth asphyxia, and severity of hyaline membrane disease (HMD). IVH followed severe HMD and was associated with cessation of the babies' own respiratory efforts while on a ventilator and also with characteristic cardiorespiratory events. The minimum arterial pressure before IVH was lower than in comparable babies who survived. It is suggested that fluctuations of systemic blood pressure from initial low levels may be important in the pathogenesis of IVH. It is possible that changes in cerebral blood flow are of even greater significance.

Intraventricular haemorrhage (IVH) is a major cause of death in low birthweight infants. The succession of new ideas about its aetiology testifies to our continuing ignorance. These ideas have included cerebral congestion at birth (Schwartz, 1927), structural vulnerability of the immature germinal matrix (Ruchensteiner and Zollner, 1929; Hemsath, 1934), maternal toxaemia (Craig, 1938), hypoxic venous congestion and capillary damage (Gruenwald, 1951), venous stasis and infarction (Larroche, 1964; Ross and Dimette, 1965; Towbin, 1968; Leech and Kohman, 1974), coagulation disorders (Gray *et al.*, 1968; Schenck *et al.*, 1968; Cade *et al.*, 1969; Thomas and Burnard, 1973), acute severe hypoxia followed by a latent interval (Harrison *et al.*, 1968), jugular compression (Vert *et al.*, 1973), venous hypertension secondary to hypoxic cardiac failure (Cole *et al.*, 1974), hypertonic alkali solutions (Simmons *et al.*, 1974; Wigglesworth *et al.*, 1975), and changes in cerebral blood flow (Wigglesworth and Pape, 1978). While theories about events before or at birth are difficult to test, theories concerning events in postnatal life can be investigated. However it is essential to distinguish events preceding IVH —and possibly contributory to it—from those occurring during and after and possibly caused by IVH. We made continuous observations for up to 3 days after birth on infants of <33 weeks' gestation or <1500 g birthweight. In this paper the clinical events of those infants who died with IVH are described and related with events to the presumed time of the haemorrhage.

Patients and methods

44 infants <1500 g birthweights or <33 weeks' gestation were studied during a 15-month period from November 1974 (Fig. 1). 17 of these babies survived and serve as controls as none of them gave evidence of acute IVH in the neonatal period or has subsequently developed sequelae—such as hydrocephalus. Necropsy was performed on all 27 babies who died; 17 died with IVH. The babies dying without IVH were not used as controls as 3 died between 6 and 8 months after birth as a result of complications experienced in the perinatal period (and are not therefore comparable with neonatal

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Table 1 *Details of babies dying with IVH and survivors*

	Babies dying with IVH (n=17)	*Survivors (n=17)*
Gestational age (weeks)	27·9 (26–32)	30·4 (27–33)
Birthweight (g)	1035 (650–1420)	1340 (630–2000)
Male : female	10 : 7	7 : 10

Figures in parentheses indicate the range.

deaths or survivors), and in only 3 of the remaining babies were arterial pressure measurements available. Details of the babies surviving and the babies dying with IVH are given in Table 1. 36 of the 44 (total study) babies had hyaline membrane disease (HMD) and 31 of these were ventilated. 16 of the 17 babies dying with IVH were ventilated because of severe HMD; IVH occurred in a baby with tracheo-oesophageal fistula after gastrostomy was performed. During the 15-month period of the study a further 47 babies of <1500 g birthweights or <33 weeks' gestation were admitted to our unit. These were not studied either because monitoring facilities were in use elsewhere, or because attempts to pass umbilical arterial catheters were unsuccessful, or because an umbilical arterial catheter passed at birth was removed only a few hours later as the clinical condition of the infant was good. Only 9 of these 47 babies died, 3 with IVH. The study group therefore did not represent the consecutive admissions in this birthweight gestational age group, and included a greater proportion of the most severely ill babies. Umbilical arterial catheters were introduced into 40 infants, generally at birth and certainly within 6 hours after birth. The catheter was passed to the level of L4 and the position confirmed by *x*-ray. Continuous arterial pressure measurements were made in 40 infants (Elcomatic pressure transducers) and recorded using a Devices M19 recorder. Mean hourly arterial pressures were derived manually by abstracting systolic and diastolic pressures from the records at 5-min intervals. The heart rate was derived either from the arterial pressure or from the ECG trace. Respiratory movements were recorded by a magnetometer (Rolfe, 1975) or by an impedance pneumograph (Air Shields Ltd), and from these, the respiratory rate was derived. A thermistor was inserted to 6 cm rectally and continuous core temperature was recorded (Electrolaboratoriet temperature recorder). In 12 infants an intravascular oxygen electrode (G. D. Searle Ltd) gave a continuous record of Pa_{O_2}. In all the infants blood-gas and pH measurements were made 4-hourly or at shorter intervals by the resident staff. Haematocrit was also measured 4-hourly on samples taken into dry syringes and measured in triplicate. Haemolysed samples were discarded. The infants were continuously observed by one of us in turn until death or recovery. Whenever a change occurred in the continuous records, any change in the infant's behaviour or environment was noted and vice versa. The occipito-frontal circumference was measured at least daily and up to 6-hourly in some infants with disposable paper tape measures.

IVH was timed by two methods described in detail elsewhere (Emerson *et al.*, 1977). Both methods depend on the effects of serial small blood transfusions given to improve tissue perfusion and oxygenation and to replace blood withdrawn for sampling. Comparison of the changes in proportions of transfused cells found in the intraventricular clot at necropsy restricted the timing of IVH to the period between two consecutive blood transfusions—'the IVH period'. By noting the rise in the proportion of transfused cells produced by infusion of a known red cell mass, changes in the baby's original red cell mass could be followed during life. A fall in fetal red cell mass occurred either before or during the period indicated by clot analysis. In this paper, 'before IVH' or 'during and after IVH' relate to the earliest time IVH could have occurred from the timing technique.

Results

Before IVH. Roberton and Tizard (1975) showed that establishment of adequate ventilation after resuscitation at birth is a powerful predictor for subsequent survival from HMD. Thus in analysing our results babies dying with IVH were divided into two groups (Fig. 1). Group 1 (n=9) were not able to support adequate ventilation from 15 minutes after birth. Group 2 (n=8) established spontaneous ventilation after resuscitation. Six of the 17 survivors were of comparable birthweights and gest-

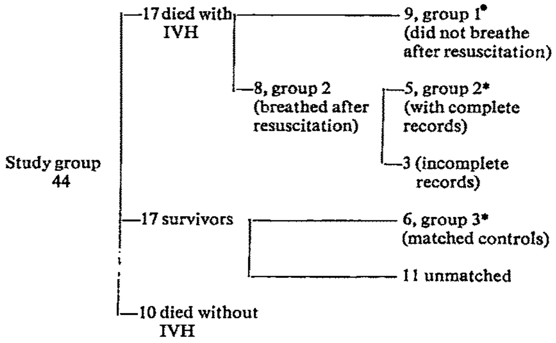

Fig. 1 *Division of the study group in order to identify comparable subgroups of babies (marked with an asterisk) who are likely to differ only with respect to factors specific for IVH (see text).*

Table 2 *Details of babies dying with IVH who breathed after initial resuscitation (group 2), and survivors matched for gestational ages (group 3)*

	Babies dying with IVH (n=5)	*Survivors (n=6)*
Gestational age (weeks)	29·1 (28–32)	29·2 (27–32)
Birthweight (g)	1153 (945–1420)	1152 (630–1860)
Male : female	4 : 1	2 : 4

Figures in parentheses indicate the range.

ations as group 2 and were ventilated for severe HMD; they are identified as group 3 (Table 2). The 9 babies in group 1 had gestational ages of 28 weeks or less and all but 2 were born by the breech. Their mothers went into labour spontaneously and preterm labour had not been anticipated. The 8 babies in group 2 and the 6 in group 3 had gestational ages of at least 28 weeks. All but one of group 2 were delivered by caesarean section for maternal indications; in group 3 there were 2 caesarean sections, one breech delivery, and 3 vertex deliveries.

In respect of the degree of birth asphyxia in each group, cord blood-gas and pH data (obtained immediately after birth from clamped sections of cord) were not sufficient to allow comparisons. Clinically, it is evident that the babies in group 1, none of whom maintained spontaneous respiration, were more severely asphyxiated at birth than those in groups 2 and 3 who initially maintained respiration after resuscitation. A comparison of groups 2 and 3 shows that at birth there were more severely asphyxiated babies in the latter—that is the survivors—but numbers are too small for statistical analysis. The core temperatures up to 6 hours after birth are shown in Table 3 for babies in groups 1, 2, and 3. The babies in group 1 had core temperatures lower at 2, 3, 5, and 6 hours after birth (P<0·05) than the remaining babies dying with IVH or survivors. Babies in groups 2 and 3 maintained similar core temperatures.

For all these reasons we considered that the babies in group 1 were different from those in groups 2 and 3 but that these last two groups are suitable for comparison. By choosing survivors of similar birthweights and gestational ages, all of whom were ventilated for severe HMD, we obtained two groups who were likely to differ only in respect to factors specific for IVH. In fact they were not comparable in respect of birth asphyxia (assessed clinically) in that the survivors (group 3) were in a poorer condition at birth than those in group 2. However all these babies (group 3) established spontaneous respiration within 15 minutes of delivery, and this appears to give a better prediction of survival than does the degree of asphyxia judged clinically. After excluding babies in whom attempts at umbilical arterial catheterisation or at timing of IVH were unsuccessful, 5 babies from group 2 were available for comparison with 6 survivors from group 3 (Table 2). Fig. 2 shows the mean hourly arterial pressures in groups 2 and 3, abstracted from the continuous records. The increase in mean arterial pressure by 6 hours after birth (estimated as a percentage change from the mean arterial pressure 2 hours after birth) was significantly greater in babies in group 2 than in group 3. Although the mean arterial pressures of the two groups were not significantly different from each other at any time after birth, this difference in relative change during the first 6 hours after birth appeared to be due to a rise in the mean arterial pressure from the low levels in babies in group 2, whereas in survivors the arterial pressure either remained stable or fell slightly. In 3 babies in group 2 there was an additional acute episode of hypotension after the first 6 hours after birth and preceding IVH. The mean of the lowest systolic arterial pressure in all 5 babies before IVH (26·8 ± 7·05 SD mmHg) was lower than the mean of the lowest systolic arterial pressure observed at any time in the 6 survivors (37·8 ± 5·9 SD mmHg). The mean of the highest blood pressure in group 2

Table 3 *Mean core temperatures at times after birth in groups 1, 2, and 3 (°C ± SD)*

Hours	*Group 1*	*Group 2*	*Group 3*
1	34·2±2·0	35·8±0·8	36·6±0·2
2	33·8±2·0*	36·0±0·9	36·1±0·2
3	34·4±1·0*	36·5±1·0	36·4±0·2
4	34·4±1·7*	36·6±0·9	36·2±0·2
5	34·6±1·6*	36·7±0·7	36·6±0·2
6	34·8±1·8*	36·8±0·9	36·9±0·1

*P<0·05 (group 1 compared with group 2).

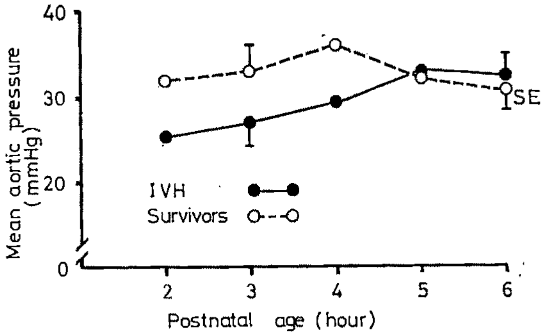

Fig. 2 *Changes in arterial pressures in babies who subsequently died with IVH and those who survived of similar gestational ages. Degree of change from the 1st to 6th hour, expressed as a percentage of the initial value, is significantly different between the two groups (P<0·05).*

Table 4 *The mean ± SD of the lowest Pa_{O_2}, highest Pa_{CO_2}, and lowest pH in groups 2 and 3 (mmHg)*

Group	*Lowest Pa_{O_2}*	*Highest Pa_{CO_2}*	*Lowest pH*
2 (n = 5)	32 ± 5·7 SD	64 ±35·0 SD	7·05 ±0·12 SD
3 (n = 6)	38 ±11·9 SD	71 ±17·8 SD	7·07 ±0·09 SD

Group 2 before IVH period; group 3 first 72 hours.

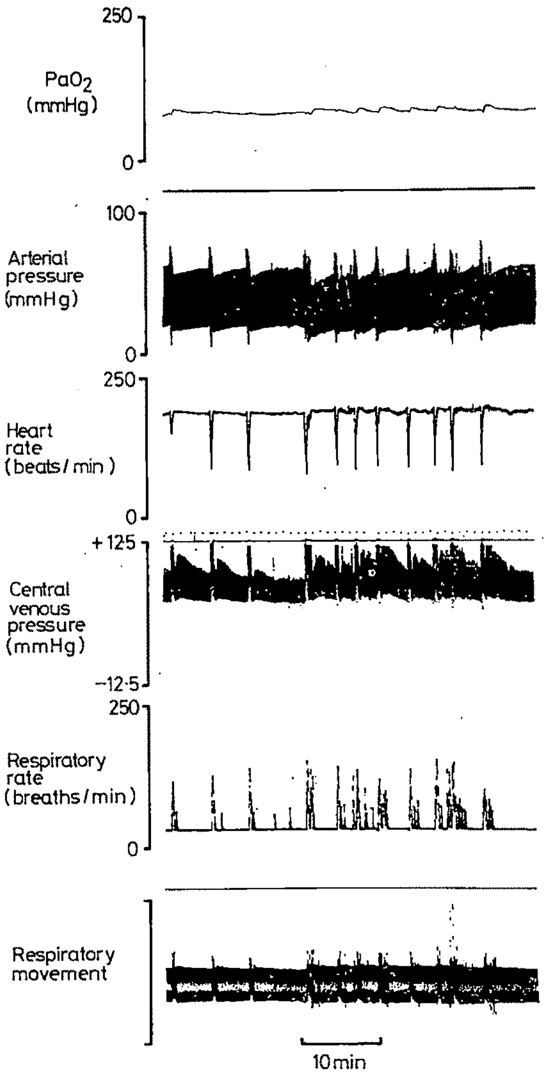

Fig. 3 *Six-channel record displaying discrete cardiorespiratory events seen only in IVH babies. The lower two traces indicate the episodic gasping movements which are accompanied by a simultaneous increase in the arterial and central venous pressures and reflex bradycardia. 11 such events appear on the record.*

was 59/34 ± 13/10 SD mmHg while it was 58/38 ± 5/6 SD mmHg in group 3.

Although all the babies in groups 2 and 3 were being mechanically ventilated and therefore attempts were being made to keep the blood-gases within acceptable limits, extremes of hypoxia and hypercapnia did occur. These extremes are shown in Table 4. The differences are not significant.

During and after IVH. In the likely consequences of IVH, babies in groups 1 and 2 did not differ from each other. The proportion of babies who had a significant fall in haematocrit, fits, or rise in anterior fontanelle tension was similar in each group. They are therefore considered together for comparison with babies surviving. Eight of the 17 babies dying with IVH had fits. In most these were tonic but occasionally a baby had a multi-focal clonic fit. Tonic fits were accompanied by pronounced cardiorespiratory events. An abrupt increase in arterial pressure accompanied by a falling heart rate was associated with a few deep inspiratory gasps, as shown in Fig. 3. In 3 babies similar cardiorespiratory events were not accompanied by visible fits. They were clearly distinguishable from fluctuations which occurred during severe acidosis in a few babies and which we interpreted as Traube-Hering waves. These cardiorespiratory events were not seen in any of the surviving babies. Examination of the respiratory wave form distinguished the babies' own respiratory efforts from movements induced by the ventilator. In 7 babies, respiratory efforts ceased during and after the IVH period. In 5 of the 17 babies (groups 1 and 2) there were dramatic cardiorespiratory events or failure of spontaneous respiratory efforts before there was any other sign of IVH. In 6 babies of the 12 in whom serial measurements of the occipito-frontal circumference were available, there was a mean increase in occipito-frontal circumference of 0·88 cm (range 0·3–1·5) after the IVH period. A mean fall in haematocrit of 0·125 (range 0·04–0·23) took place in the 12 babies in whom serial haematocrit measurements were available. A rise in anterior

Table 5 *Amounts of sodium bicarbonate (mmol) and THAM (ml) infused before, and during and after the IVH period*

	Group 2 (n = 5)		*Group 3 (n = 6)*
	Before IVH	*During and after IVH*	*Total in first 72 hours*
Sodium bicarbonate (mmol) Mean	2·1	5·6	6·7
THAM (ml) Mean	2·0	17·8	0·4

fontanelle tension as detected by palpation was noted in 8 babies. A sudden fall in pH to a value of <7·1 occurred in 8 babies Table 5 shows the alkali infused into babies of groups 2 and 3. It can be seen that the amounts of bicarbonate solution and tromethamine (THAM) were no different before the IVH period in group 2 from the totals given to group 3 but were much greater (THAM) during or after the IVH period The mean hourly infusion of base (1 mmol of sodium bicarbonate equivalent to 1 ml 6% THAM) before the IVH period in group 2 was 0·09 ml/kg per hour. In group 3 this was 0·08 ml/kg per hour for the first 72 hours

Discussion

The ability of an infant to breathe adequately within 15 minutes of birth was used to separate infants who subsequently had IVH into two groups; these groups differed from each other in other ways. The infants who were not able to support adequate ventilation within 15 minutes of birth (group 1) were of gestational ages 28 weeks or less and were acidotic at birth, usually considerably so. With the exception of one baby, all were born by the breech; this may reflect their prematurity and it has implications for the fate of premature infants who are to be born by the breech.

Babies in group 1 had significantly lower core temperatures in the first 6 hours after birth. Hypoxia and acidosis inhibit thermogenesis by brown fat (Oliver and Karlberg, 1963; Scopes and Ahmed, 1966). While we cannot be sure that the asphyxiated babies were not subjected to more cold stress during resuscitation after birth than the rest—particularly during umbilical catheterisation at birth—it is possible that the lower core temperature is due in part to inhibition of nonshivering thermogenesis. In the babies of group 1, the onset of IVH ranged from <2 to 21 hours after birth, estimated by the proportion of transfused cells in the IVH. IVH occurred despite rapid correction of hypothermia, hypotension, and acidosis. We suggest that the causes of IVH in this group operate before and during birth.

By contrast babies in group 2 who were of gestational ages of at least 28 weeks were nearly all delivered by elective caesarean section for maternal indications. They were not as asphyxiated at birth and all but one developed severe HMD. The onsets of the IVH periods in this group ranged from 12 to 72 hours after birth and were later than the onsets in group 1. In babies of group 2 it is reasonable to look for the causes of IVH after birth. Comparison with babies in group 3 which should identify factors specific for IVH has allowed us to test current hypotheses concerning the aetiology of this condition. It has been suggested, for example, that IVH may be precipitated by alkali administration (Simmons *et al.*, 1974; Wigglesworth, *et al.* 1975). The technique of timing the earliest occurrence of IVH allows comparisons to be made of the alkali administration before IVH rather than the administration needed as a consequence of IVH. The babies of group 2 who subsequently developed IVH were given no more alkali before the IVH period than surviving babies; some of them received no alkali before the IVH period.

Although babies in group 1 had core temperatures significantly lower than babies in group 2, babies in group 2 had similar core temperatures as survivors. Hypothermia therefore is unlikely to predispose to IVH. Similarly the greatest arterial pressure observed in babies subsequently dying with IVH was identical with that of babies surviving, and the extremes of blood-gases were no different in the two groups either, suggesting that hypoxia, hypercarbia, and acidosis were not specific factors in the aetiology of IVH. It would appear that IVH can occur in the presence of normal arterial pressure.

The pronounced cardiorespiratory events which took place at the time of IVH were associated with tonic movements and were thought to be a consequence of seizure activity. The importance of timing of IVH is seen in evaluating these events. As in 2 babies the cardiorespiratory events occurred before and in 3 babies they occurred during the IVH period, it is tempting to ascribe to them an aetiological role. However, in 3 babies they took place after the fall in fetal red cell mass and it is probable therefore that they occurred as a consequence rather than as a cause of IVH. The only distinguishing feature that emerged from our comparison of events before the IVH period in babies in group 2 with events in babies in group 3 was that of hypotension. Although there is no evidence to support the suggestion that this is a causative relationship, we suggest that any hypothesis for the cause of IVH should take this finding into account. It is suggested that resulting from severe birth asphyxia, IVH babies may be subjected to cerebral ischaemic hypoxia, and then on restoration of normal arterial pressure there are areas of 'luxury perfusion' in the subependymal layer sufficient to initiate subependymal haemorrhage. This then ruptures into the lateral ventricles. It is possible that cerebral blood flow is of more critical importance than systemic blood pressure, but the relationship between these two variables in the newborn has yet to be determined (Cooke *et al.*, 1977).

Turning to the events that took place during and after IVH, failure on the part of the baby to continue making spontaneous respiratory movements, while on the ventilator, was an equally reliable sign of IVH and accords with general clinical experience. A fall in haematocrit was a consistent finding during and after IVH and occurred either alone or in combination either with a rise in anterior fontanelle tension or with fits in 15 of the 17 babies dying with IVH. In addition, a fall in fetal red cell mass took place at the same time as the onset of other signs of IVH and was not observed in any surviving baby. Where a blood transfusion is given after the onset of IVH the diagnosis can be made during life, and is nearly always supported by close observations of clinical events.

The patients were under the care of Drs J. D. Baum, B. N. Bower, H. Ellis, M. Moncrieff, and D. Pickering, We should like to thank Dr P. Rolfe and Mr P. Sutton for their bioengineering assistance and Miss P. Townshend and her nursing colleagues for their help. P.H. was in receipt of a grant from the Medical Research Council (GE974–185c), and D.M.S. from the Sir William Coxen Trust Fund; M.F. was a British Council scholar.

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Effect of feeding on neonatal oxygen consumption

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SUMMARY Oxygen consumption was measured in 9 short-gestation infants before feeding and for an hour after, using a closed-circuit metabolism chamber. Using the same system, O_2 consumption of 9 term infants was measured for varying periods, beginning one hour from the end of the last feed. In the short-gestation infants a rise was found in the 15–45 minutes after feeding; O_2 consumption then fell, and after 60 minutes had reached prefeed levels. The term infants showed no decrease with time after the first hour, as would be expected if the effect of feeding on O_2 consumption extended beyond this. It is concluded that increased O_2 demand after appropriate feeding does not extend beyond one hour postprandially.

The first quantitative description of the effect of feeding on oxygen consumption ($\dot{V}O_2$) was reported by Lavoisier (1789). He found that, in a temperature of 32°C, $\dot{V}O_2$ of an adult rose about 50% above the resting value during digestion. Bidder and Schmidt (1877) attributed this rise to the 'work of digestion'. This concept of increased intestinal work was challenged by Benidict and Emmes (1912), who showed that $\dot{V}O_2$ rose equally in response to either intravenous or oral amino-acids. A succinct summary of the various theories of the cause of this rise was written by Kleiber (1961). Rubner (1902) introduced the term 'spezifischdynamische Wirkung', which possibly by mistranslation has become specific dynamic action (SDA).

Early measurements of SDA in infants were made by Rubner and Heubner in 1899. Unfortunately, they compared the metabolic rate of a healthy 7½-month-old girl with that of a malnourished boy of 3½ months, being then unaware of the effect of age and state of nutrition on basal metabolism. Techniques of measurement have now improved and Murlin *et al.* (1925) reported that the SDA of ordinary 'feedings' within the first 8 days of life was small, the largest increase being 12% after a feed of 12% lactose. Since then a variety of workers using different foods and in differing environments have reported increases from 6% (Levine *et al.*, 1927) to 32% (Gamalero and Crosato, 1958). Městyán *et al.* (1969) investigated the magnitude and thermoregulatory significance of the response to feeding in premature babies under carefully controlled conditions, and found an increase in metabolism of 30% after feeding a milk formula in a thermoneutral environment. Gentz *et al.* (1970), studying the influence of feeding in newborn pigs, reported that in previously unfed piglets there was a significant rise in $\dot{V}O_2$ after feeding: the maximum increase was about 45%. They did not, however, find the rise in those previously fed to be significant, although from their figures it was of the order of 10%. Gentz *et al.* (1976) also investigated short-gestation infants and those of diabetic and prediabetic mothers and reported a 10 to 30% rise in $\dot{V}O_2$ after feeding.

The length of time during which the rise persisted in the series of Městyán *et al.* (1969) was about 240 minutes, although prefeed values were approached about 150 minutes postprandially. In the piglets (Gentz *et al.*, 1970) the return to mean control values was about 500 minutes in the previously fasted group; no values were given for the previously fed piglets. The $\dot{V}O_2$ of infants (Gentz *et al.*, 1976) reached a maximum at 1 to 1½ hours and then slowly returned to prefeed values. In none of these series was sleep state taken into account. In the human infant this can have a significant effect on $\dot{V}O_2$ (Stothers and Warner, 1978).

If these figures of duration of response are a consistent feature of neonatal feeding, it would seem that the infant spends little time with a basal $\dot{V}O_2$, and that feeding imposes an almost constant increase in oxygen demand. The aims of the present study were to observe the effect of feeding on $\dot{V}O_2$ with special reference to the length of time such an effect persisted, and to observe if the variation of

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$\dot{V}O_2$ with sleep state in the short-gestation infant was similar to that of the term infant in a thermoneutral environment.

Material and methods

$\dot{V}O_2$ was measured in the closed-circuit metabolism chamber described by Hill and Rahimtulla (1965), modified by Hey and Katz (1969). The infants were from the maternity wards and the special baby care unit of this hospital. Each baby was studied with the informed consent of the mother and usually in her presence. Because it was considered unethical to administer nasogastric feeds to normal, term infants, two separate studies were undertaken.

In the first series 9 short-gestation but otherwise well infants were measured (Table 1). At the time of measurement all were being nasogastrically fed. In the second, observations were made of 9 term babies, 8 of whom were being breast fed and one bottle fed, all on demand. In both studies the infants were measured prone, in a thermoneutral environment, the appropriate temperature having been calculated from the data of Hey (1969). In each case the rectal temperature was measured throughout the period of observation. Minute-by-minute records of behavioural states were made by an experienced observer, continuously watching the infant for body and eye movements. Periods which contained more than one significant movement, such as a stretch, in any one minute, were excluded from the results in the first series and only used in the preliminary analysis of the second.

The short-gestation infants were placed in the metabolism chamber and the feeding tube attached to a connector which penetrated the door in an air-tight fashion, with a 3-way tap on the outside. In order to standardise the rate of administration, for each hour between feeds, 5 minutes of feeding time were allowed; therefore, if the infant was being fed 2-hourly, the feed would be given over a period of 10 minutes. A volume of air equal to the volume of feed was extracted from the chamber simultaneously using a reciprocating pump. In 7 of these infants, measurement of $\dot{V}O_2$ in adjacent REM and NREM sleep states lasting for at least 8 minutes was possible during the 2nd postprandial hour.

In the second series $\dot{V}O_2$ of 9 healthy, term infants was measured; 3 of them were girls. Mean age was 3·5 days (range 2–5) and mean weight 3·1 kg (range 2·6–3·7). The measurements were begun 60 minutes after the end of feeding and continued for as long as the infant remained asleep.

Minute-by-minute values were obtained from the traces and these data were converted into ml O_2 consumed per minute, at standard temperature and pressure, dry. In the case of the short-gestation group, comparison was made of the differences in $\dot{V}O_2$ at four time intervals from the prefeed values using a related t test. The individual minute $\dot{V}O_2$ values of the term infants were subjected to a single mathematical 'smoothing' (A. Hyams, 1977, personal communication) based on binomial weightings, in an attempt to observe any patterns or overall trends. The minute-by-minute values were then linearly regressed for the entire period of observation, irrespective of slight movement of sleep state. Finally, a second linear regression was calculated, periods of NREM sleep and those containing significant movement having been excluded.

Results

Short-gestation infants.

Sleep states and $\dot{V}O_2$

A substantial increase in $\dot{V}O_2$ accompanied the change from NREM sleep to REM sleep (Table 2). This was diminished when no regard was taken of the direction of change, but was still significant. When REM sleep preceded NREM, the change in $\dot{V}O_2$ was not significant.

Table 1 *Details of the short-gestation infants, and the maximum increase in $\dot{V}O_2$ in the 15- to 45-minute period, expressed as a percentage of the prefeed level*

Case	*Gestational age (weeks)*	*Weight (kg)*	*Age (days)*	*Frequency of feed (hours)*	*Volume (ml)*	*Type of feed*	*Rise in $\dot{V}O_2$ (%)*
1	36	1·65*	6	2	45	EBM	7·6
2	35	3·5†	13	3	60	F	17·8
3	35	1·36*	20	2	25	F	3·5
4	32	1·47	14	1	15	F	13·7
5	34	1·63	11	2	25	EBM	10·0
6	36	2·51	6	3	60	F	10·4
7	32	1·48	10	1	13	EBM	20·3
8	34	1·57	12	2	27	F	51·2
9	35	2·31	25	2	35	F	36·7

*Below 2 SDs from expected mean (Usher and McLean, 1969); †diabetic mother.
EBM = expressed breast milk; F = formula.

Table 2 *Effect of REM and NREM sleep on* $\dot{V}O_2$

Direction of sleep state change	*No. of infants**	*REM* $\dot{V}O_2$ *ml/min*	*NREM* $\dot{V}O_2$ *ml/min*	*Increase in REM sleep (%)*	*P*
NREM ⇄ REM	7	6·75	6·08	11	<0·05
NREM → REM	5	6·68	5·83	15	<0·01
REM → NREM	5	6·94	6·6	5	>0·05

*Details of the 7 infants

	Weight (kg)	*Age when studied (days)*	*Gestational age (weeks)*
Mean	2·23	16	34·7
Range	1·35–3·5	6–26	33–36

Postprandial metabolism

Because of the above observation, comparative measurements included in this series were made when the infants were in quiet REM sleep. With the exclusion of movement and NREM sleep from the periods of observation, only one of the 9 infants had continuous data for the full pre- and interfeed period (Fig. 1). Fig. 2 shows the results from eligible traces at the following times: prefeed, 0–15, 15–45, 45–60, and >60 minutes postprandially.

During the 15–45-minute period $\dot{V}O_2$ was significantly increased; the mean rise was 13%. A return to basal levels was achieved within the first hour. Rectal temperature change was greatest in the 15- to 45-minute period, with a mean rise over prefeed levels of 0·17°C (range 0–0·3). By 60 minutes postprandially this had diminished to 0·01°C (range 0–0·2).

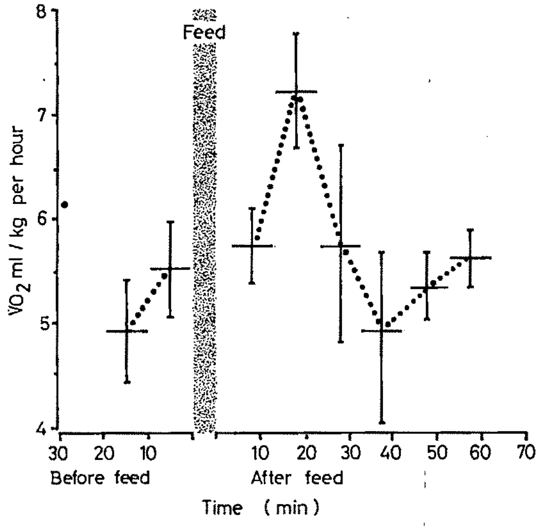

Fig. 1 *O₂ consumption of one short gestation infant who remained still, and in REM sleep throughout the pre- and interfeed periods. Only the 15- to the 45-minute period was significantly different from prefeed level (maximum difference 31%)*

Term infants.

Postprandial metabolism

Fig. 3 shows the original minute-by-minute $\dot{V}O_2$ of a term infant measured from 60 to 240 minutes after the end of a feed. Superimposed is the result of a single 'smoothing' manoeuvre. A gradual diminution of $\dot{V}O_2$ with time during each NREM sleep period was observed, as was the variability associated with movement. Visually, however, there was no obvious overall trend during the 3 hours of observation.

Details of linear regression of $\dot{V}O_2$ with time, without regard to sleep state or movement are given in Table 3. There was no significant difference in the slopes from horizontal when the group was considered as a whole. Exclusion of periods of movement and of NREM sleep did not alter the results significantly.

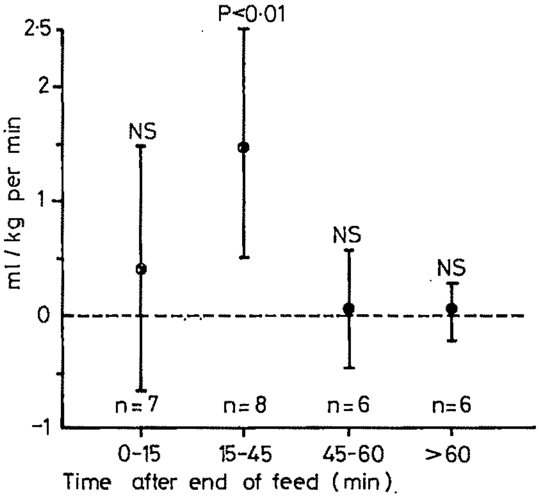

Fig. 2 *Results of pooled data from the 9 short-gestation infants. Means of the differences from the prefeed (0) levels are shown with the SDs. Only the 15- to 45-minute period is significantly different.*

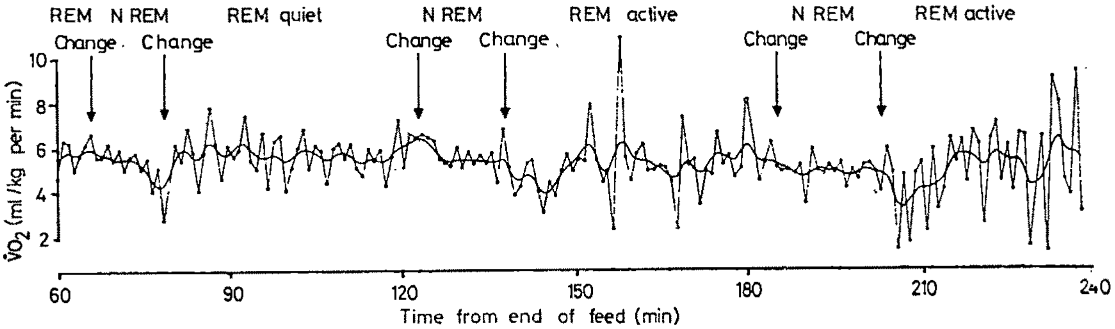

Fig. 3 *Minute-by-minute O_2 consumption ( ) of a 2·9 kg breast-fed infant aged 2 days. The result of a single smoothing (/V) is superimposed. In this case the slope value was not significantly different from zero ($B = -0·0023$)*

Table 3 *Individual results of the linear regressions of $\dot{V}O_2$ on time. A negative value of B, the slope of the regression line, represents a diminution of $\dot{V}O_2$ with time, and a positive value an increase*

Case	*No. of observations (min)*	*B value*	*Confidence limits*		*P*†	*Change in temperature**
			Upper	*Lower*		
10	126	0·0011	0·0038	−0·0016	NS	−0·05
11	117	0·0011	0·0074	−0·0051	NS	−0·1
12	89	0·0070	0·0115	0·0026	1%	+0·1
13	180	−0·0023	0·0004	−0·0050	NS	+0·3
14	91	−0·0043	0·0105	−0·0190	NS	−0·05
15	139	0·0009	0·0050	−0·0031	NS	−0·2
16	66	0·0099	0·0248	−0·0049	NS	+0·1
17	223	0·0053	0·0079	0·0027	1%	+0·3
18	110	−0·0032	0·0036	−0·0101	NS	+0·2

*Rectal-environmental temperature change (°C) over the period of observation; †statistical comparison of the slope of the line with respect to B = 0; i.e. a horizontal line.

The rectal temperatures showed neither significant nor consistent directional change during the periods of observation (Table 3).

Discussion

The fact that $\dot{V}O_2$ increases in REM sleep in premature infants is in keeping with the findings of Scopes and Ahmed (1966), and also in agreement with our own findings in term infants (Stothers and Warner, 1978). It is interesting that the magnitude of maximum change (15%) was considerably greater than the 6·6% rise found in the latter series, and emphasises the fact that when comparative $\dot{V}O_2$ measurements are being made over fairly short periods of time, note should be taken of sleep states.

The results from the feeding series support previous workers' findings of a rise in $\dot{V}O_2$ postprandially. From the small sample of short-gestation infants measured just before and after gavage feeding the magnitude of the rise appeared highly variable, ranging from 4 to 50% of the resting values. This large variation may have been due to several factors. The effect of age on resting metabolism is well established, but the importance of the effect of the energy content of the food, the state of nutrition, and growth rate on the size of response is less widely accepted.

Evidence that these factors are of major importance is however accumulating. In 1966 Krieger found that insensible water loss, which she used as an index of metabolic rate, increased after feeding only during periods of weight gain in infants aged between 5 and 43 months. No such increase was observed when weight was either static or decreasing. Ashworth (1969) using indirect, open-circuit calorimetry measured the effect of feeding on 8 malnourished infants aged between 10 and 36 months and reported that during the 'catch-up' phase, or period of rapid growth, the metabolic rate increased significantly. Once the growth rate had returned to normal there was no such increase. She concluded that in the case of the starved infants the classic concept of SDA did not apply and that the size of increase in metabolic rate after a meal was related to 'the energy cost of growth and, in particular, to the energy cost of protein synthesis'. This theory has now been convincingly supported by Gentz *et al.* (1976) who reported measurements of $\dot{V}O_2$ and respiratory quotient (RQ) of 5 infants aged between 2 and 11 days who were either small-for-dates or of diabetic mothers. A rise in both variables was observed after feeding, and it was suggested that the most likely cause was protein synthesis and lipogenesis. Thus the simple concept of SDA proposed by Voit (1901) as food being fuel for the metabolic fire could be made compatible with modern views if one introduces Ashworth's 'energy cost of growth' as a variable 'fanning' of the flames.

In the present studies the duration of the response was more consistent. All of the babies in the first series regained prefeed $\dot{V}O_2$ values within the first hour from the end of the feed. In general this is in agreement with Brooke's findings (O. Brooke, 1978, personal communication). Support for this observation was obtained from the term infants in whom $\dot{V}O_2$ did not diminish consistently with time, as one would expect if significant effects exceeded one hour. This is in contrast with the findings previously reported in newborn babies (Městyán *et al.*, 1969; Gentz *et al.*, 1976), and piglets (Gentz *et al.*, 1970) in which considerably longer 'recovery' periods were observed. Explanation of the apparent conflict necessitates further examination of those series.

Only group 1 of the infants of Městyán *et al.* (1969) were nursed in thermoneutrality. These preterm infants had an interfeed period of 4 hours. The ages of their 8 infants ranged from 6 to 24 days and their weights from 1300 to 2100 g. 40 to 60 ml milk were given, an amount per feed which is considerably greater than that given in the present series, although the daily volumes were approximately equal. The longer interfeed intervals and the increased volumes may explain the longer 'recovery' periods. The range of changes of $\dot{V}O_2$ was similar to our own series (11–44%), but the mean was higher (30%).

The study by Gentz *et al.* (1970) comprised fed and unfed piglets. The maximum rise in $\dot{V}O_2$ and the lengthy duration of the effect were found in the unfed group, which is not comparable with the infants in the present study, all of whom had been previously and recently fed. In his fed group, however, there was a rise of about 10%, which because of individual variation did not reach statistical significance. In addition, the peak $\dot{V}O_2$ values appear to have been reached some 30 minutes after administration of the sows' milk. The length of time taken to return to prefeed $\dot{V}O_2$ levels was not reported.

Full details of the volume and interfeed intervals of the babies in Gentz's series unfortunately were not reported (Gentz *et al.*, 1976). It is interesting to note, however, that the pattern of response was similar to that reported by Městyán *et al.* (1969), suggesting a similarity of feeding regimens; the maximum rise in $\dot{V}O_2$ occurring in the 60- to 90-minute period postprandially with a subsequent, gradual return to prefeed levels.

Our results suggest that the response to feeding is highly variable, but that in 'appropriately-fed' infants the effects should not exceed an hour. Great difficulty arises, however, in the interpretation of 'appropriate'. No firm rules of the volume or frequency with which short-gestation infants should be fed can be made from this small study. It only supports the advocates of 'a little and often'. In the healthy, term, demand-fed babies the recovery period was within an hour, suggesting that the infant knows best the appropriate volume and timing, supporting the protagonists of demand feeding.

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Erratum

Clinical evaluation and comparison of the Infrasonde, Arteriosonde, and mercury sphygmomanometer in measurement of blood pressure in children. J. M. Savage, M. J. Dillon, and J. F. N. Taylor.

It is regretted that in the March issue (*Archives*, 1979, **54**, 187–188) the legends to Figs 7 and 8 were transposed.

Archives of Diseases in Childhood, 1979, **54**, 421–426

Hearing loss in very low birthweight infants treated with neonatal intensive care

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SUMMARY The hearing of 111 perinatal intensive care survivors of birthweights 1500 g or less was assessed at a mean age of 6½ years (range 4–12). These 111 infants included 86% of the long-term survivors of this birthweight cared for in the newborn unit of University College Hospital, London, during the years 1966–72. All these infants were nursed in commercially available incubators for periods ranging from 2 to 80 days (mean 37) in which the mean noise threshold was 65 dB. Ten (9%) had sensory neural hearing losses, one (1%) infant had a congenital conductive hearing loss, and 21.(19%) infants had exudative otitis media with a mean loss of 25 dB. Apnoeic attacks in the neonatal period were the most significant predictors of hearing loss in these infants ($P<0\cdot05$) and an indirect serum bilirubin level of at least 170 μmol/l (10 mg/100 ml) in the neonatal period had an additive effect ($P<0\cdot05$). There was no evidence that ambient noise had affected the hearing of these very low birthweight infants.

Reports indicate that the incidence of sensory-neural hearing loss among very low birthweight infants is high (4 to 15·9%) (Campanelli *et al.*, 1958; McDonald, 1964). Douek *et al.* (1976) suggested that this might be due to damage of the cochlea by ambient noise from the incubators in which these infants are usually nursed. To support this suggestion they quoted a study by Campanelli *et al.* (1958) which showed that the mean length of stay in incubators for low birthweight infants with sensory neural loss was significantly longer than the mean for low birthweight infants without hearing loss. There were, however, other important differences between the two groups. In particular, the mean birthweight in children with sensory neural hearing loss was only 981 g, whereas the mean for the children without hearing loss was much greater—1718 g ($P<0\cdot05$).

The incidence of potentially lethal or damaging perinatal complications increases as birthweight and gestation decrease. Thus, the infants in the study of Campanelli *et al.* (1958) who had sensory neural hearing loss are much more likely to have suffered brain damaging complications than the heavier infants without hearing loss. Perinatal complications are also likely to influence the length of incubator stay. Thus it is important to investigate the potential role of all these factors in the aetiology of sensory neural hearing loss before attempting to apportion blame.

Population

During the years 1966–72, 273 infants of birthweights 1500 g or less were admitted to University College Hospital (UCH) for neonatal intensive care. 164 were born in UCH, 99 were referred from other hospitals, and 10 were admitted from home where they had been born unexpectedly. 132 (48%) of these infants survived. 129 of the surviving infants were followed up for more than 5 years, 2 were lost to follow-up, and one child died after a domestic accident at age 4 years.

Methods

The management of the infants during the perinatal period and at follow-up after leaving hospital has been described (Stewart and Reynolds, 1974;

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Stewart *et al.*, 1977; Turcan *et al.*, 1977). Methods included a high standard of obstetric care, prompt resuscitation at birth and subsequently, prevention if at all possible of hypoxia, hypothermia, hypoglycaemia, hyperbilirubinaemia, and infection; and the provision of warmth and adequate nutrition.

All the children were nursed in standard, commercially available incubators until their weights were >1500 g. Noise levels in these incubators under normal working conditions in the neonatal unit were tested using a Dawe octave band sound level meter. The noise levels in 9 incubators of 4 types which had been in use in UCH for at least 10 years, including the years that the children being studied were born, varied from 58 to 72 dB on all weightings of the octave band sound level meter. The mean threshold was 65 dB sound pressure level. The mean threshold on A weighting was 62 dB, on B weighting 65 dB, on C weighting 67 dB, and D 66 dB. The noise level outside the incubators was 65–75 dB sound pressure level on all weightings.

After leaving hospital the children were seen regularly for clinical and neurological assessments, including otoscopic examination and developmental testing. Psychometric measurements were made at 3½, 5, and 8 years; these included educational and attainment tests, and assessment of motor skills for the older children. Hearing responses were elicited in the course of developmental testing, and children in whom satisfactory responses could not be obtained by age 9 months were referred for detailed testing, using 'distraction' techniques and objective hearing testing, using the posterior auricular muscle (PAM) response method (Fraser *et al.*, 1978), in the audiological unit of the Royal Ear Hospital, UCH.

Pure tone audiometry within the speech frequencies (250–8000 Hz) was tested on all children who were able to co-operate sufficiently to give a reliable response at ages ranging from 4 to 12 years. The function of pure tone audiometry was to compare the hearing of the child with accepted hearing levels for normal subjects (International Standards Organisation). Thus, a mean loss of >20 dB in the speech frequencies was considered to be abnormal. Among children unable to co-operate, usually because of other serious handicaps—such as mental retardation—the hearing threshold was evaluated using free field audiometry, the PAM response method (Fraser *et al.*, 1978), and transtympanic electrocochleography (ECOG) (Beagley *et al.*, 1974).

Results

The hearing threshold was elicited in 111 of the 129 children. Pure tone audiograms were obtained from 107 children at a mean age of 6½ years (range 4–12).

In one very retarded child the threshold was obtained with pure tone audiometry in free field, and 3 children were assessed with PAM or ECOG. No audiogram was obtained from 18 children, comprising 14 who were living abroad and 4 whose parents did not co-operate. All these 18 children had developed normal speech and were considered by their local medical practitioners, teachers, and parents to have normal hearing. In the group of 111 children in whom the hearing threshold was elicited, one child had congenital conductive hearing loss, 21 (19%) had exudative otitis media with mean hearing loss of 26 dB, and 10 (9%) had sensory neural hearing loss. Of these 10 children, 8 had bilateral losses in the speech frequencies (250–8000 Hz) which varied from 35–80 dB (mean 51). Four of the 8 were seriously handicapped by their hearing loss and required special education. The other 4 were able to compensate for the loss with hearing aids and remedial help, and attended normal schools. Two other children had unilateral losses, including one with a loss of 70 dB at 8000 Hz only, but both these children had hearing which was adequate to perceive speech without difficulty.

The distributions of birthweight, period of gestation, sex, single or multiple pregnancy, place of birth, or method of delivery were the same for children with or without sensory neural hearing loss (Tables 1 and 2). Records for length of stay in the incubator were only available for the 56 infants, including 7 with sensory neural hearing loss, who were born in the years 1968–69 and 1971–72. (Records

Table 1 *Perinatal characteristics of 10 children with and of 101 children without sensory neural hearing loss, birthweights$\leqslant$1500 g*

	Sensory neural hearing loss	
	Present (n=10)	*Absent (n=101)*
Boys	5	43
Girls	5	58
Singletons	5	79
Multiple births	5	22
Born in UCH	5	68
Referred	5	33
Birthweight		
Appropriate for gestational age	9	76
Small for gestational age	1	25
Method of delivery		
Vertex	5	42
Forceps	3	20
Breech	2	19
Caesarean section	0	20

for the other years were destroyed in a flood during the preparation of these data.) There was no significant difference between the length of stay for the children with or without sensory neural hearing loss among the 56 children ($P<0{\cdot}1$) (Table 2).

The incidences of perinatal complications in the children with or without sensory neural hearing loss are shown in Table 3. Two complications—apnoeic spells in the neonatal period that were sufficiently severe to require treatment with mechanical ventilation, and a serum bilirubin level of at least 170 µmol/l in the neonatal period were present more often in children with sensory neural hearing loss than in those without. However, the difference was only significant in the children who had apnoeic spells ($P<0{\cdot}025$). The mean maximum serum bilirubin level among the 6 jaundiced children with sensory neural hearing loss was greater than the mean among the 28 jaundiced children without hearing loss, but this difference was also not significant ($P<0{\cdot}2$).

Only one (10%) of the 10 children with sensory neural hearing loss had cerebral palsy. This incidence did not differ significantly from that for the 101 (4%) children without hearing loss.

All the children in the study had a psychological assessment at 3½ years. To accommodate the varying skills of such children, one of three different tests was chosen. It was, therefore, not possible to calculate mean scores, but the distribution of the SD grouping was significantly lower in the 10 children with sensory neural hearing loss than in those without ($P<0{\cdot}05$). 55 of the children were aged at least 8 years and were assessed on the (WISC) IQ scale. There were highly significant differences between the means of the performance, verbal, and full-scale scores in this test for the 6 children with sensory neural hearing loss and for the 49 without such loss ($P<0{\cdot}001$) (Table 2). This indicated an overall depressed level of functioning for the children with sensory neural hearing loss and suggested that these children may have suffered additional cerebral

Table 2 *Neonatal and developmental characteristics of 10 children with and of 101 children without sensory neural hearing loss, birthweights ⩽1500 g*

	Sensory neural hearing loss		*Significance of difference*
	Present (n=10)	*Absent (n=101)*	
Mean birthweight (g)	1199	1266	NS
Mean gestation (weeks)	29·8	30·8	NS
Mean pH within 2 hours of birth	7·20	7·24 (n=74)	NS
Mean serum bilirubin level for infants with a value >170 µmol/l	272	238 (n=29)	NS
Mean duration of incubator care (days) (1968–69 and 1971–72 only)	45·4 (n=7)	36 (n=49)	NS
Mean full-scale IQ(WISC)	75± 8·7 (n=6)	97±19·6 (n=49)	P<0·001
Verbal scale	74± 7·8 (n=6)	98±16 (n=46)	P<0·001
Performance scale	80±13·2 (n=6)	101±12·6 (n=46)	P<0·001

Table 3 *Neonatal illnesses and drug treatment in 10 children with and 101 children without sensory neural hearing loss, birthweights ⩽1500 g*

	Sensory neural hearing loss		*Significance of difference*
	Present (n=10)	*Absent (n=101)*	
Intrapartum hypoxia			
Heart rate <100 at birth	2	27	NS
pH <7·2 (within 2 h)	3(n=5)	28(n=74)	NS
Negative base excess >15 mmol/l (within 2 h)	0(n=5)	6(n=75)	NS
Neonatal illness			
Hyaline membrane disease	4	35	NS
Apnoea needing intubation ± ventilation	6	22	P <0·025
Bilirubin >170 µmol/l	6	29	P <0·1
'Dextrostix' <25	1	14	NS
Infections			
Rubella } Intrauterine	1	2	
CMV	0	0	NS
Meningitis } Postpartum	1*	1	
Septicaemia	0	1	NS
Ototoxic drugs			
Streptomycin (1966–68)	2(n=4)	11(n=38)	NS
Kanamycin (1967–71)	2(n=5)	20(n=63)	NS
Gentamicin (1971–72)	1(n=1)	9(n=30)	NS

*Aged 2 years.

Table 4 *Neonatal and developmental details of 10 children with sensory neural hearing loss, birthweights ≤1500 g*

Case	*Pregnancy*	*Sex*	*Birthweight (g)*	*Gestation (weeks)*	*Birthweight/gestational age*	*Intrapartum hypoxia*	*Neonatal hypoxia*	*Bilirubinaemia (µmol/l)*	*Infection*	*Incubator care (days)*	*Cerebral palsy*	*Visual defect*	*IQ Verbal*	*IQ Performance*	*IQ Full scale*	*Attainment*
'Handicapped' and requiring special education																
1	Twin	M	1500	31	AGA	Apex beat <100 pH <7·2	Apnoea	187	Nil	49	Nil	Nil	65	76	67*	Slow learner
2	Single	M	910	26	AGA	pH <7·2	Nil	289	Nil	46	Nil	Nil	—	—	110†	Appropriate
3	Twin	F	1220	35	SGA	Nil	Apnoea (MV)	289	Rubella	34	'Clumsy'	Nil	—	—	100†	Appropriate
4	Quad	M	1310	30	AGA	Nil	Apnoea (MV)	153	Nil	49	Nil	RLF	—	—	100†	?Slow learner
'Compensated' by the use of hearing aids and remedial help in normal schools																
5	Single	F	1435	32	AGA	Nil	Apnoea	187	Nil	—	'Clumsy'	Nil	71	72	70*	Learning difficulties
6	Single	F	1446	32	AGA	Nil	Nil	340	Nil	—	Nil	Nil	69	75	69	Slow learner
7	Single	F	850	26	AGA	pH <7·2	Apnoea (BE = −23)	Nil	Nil	—	Nil	Nil	72	92	80*	Learning difficulties
8	Single	M	1090	28	AGA	Nil	Apnoea (MV)	Nil	Nil	64	Yes	Nil	85	65	73	Appropriate
Unilateral loss, hearing adequate for the perception of speech																
9	Twin	M	1030	28	AGA	Apex beat <100	Nil	Nil	Nil	41	Nil	Nil	82	100	90*	Learning difficulties
10	Twin	F	1200	30	AGA	Nil	Nil	349 (Rh affected)	Meningitis (aged 2 years)	35	Nil	Squint	—	—	94‡	Appropriate

*WISC at 8 years; †provisional score on Merrill-Palmer scale; ‡Stanford Binet at 3½ years. AGA = appropriate for gestational age, SGA = small for gestational age, RLF = retrolental fibroplasia, MV = mechanical ventilation.

insults. This was also suggested by the finding that 7 of the 10 children with sensory neural hearing loss were receiving extra help in school for such difficulties as distractability, overall delay, and manual control, as well as those due to their hearing loss. Data on the 10 children with sensory neural hearing loss are summarised in Table 4.

To investigate the aetiology of sensory neural hearing loss in this group of children, analysis of variance with stepwise regression was carried out using 29 social, obstetric, and perinatal variables. 25 (22%) of the 29 variables contributed significantly to the sensory neural hearing loss. The most important contribution (5% of the variance) was made by apnoeic spells occurring in the newborn period; this variable was the only one that made a significant independent contribution ($P<0 \cdot 05$). Four other variables—mechanical ventilation, jaundice (defined as a serum bilirubin $\geqslant$ 170 μmol/l), duration of incubator stay, and method of feeding—made significant additional contributions. However the treatment variables—mechanical ventilation, duration of incubator stay, and method of feeding—were significantly correlated with many of the illness variables. In order to try to separate the effects of the methods themselves and the conditions for which they were given, the variables were grouped into those concerning the antenatal period, perinatal illness, or treatment, and the regression was repeated. On this occasion, only 10 of the 11 variables concerning perinatal illness proved to be significant predictors of sensory neural hearing loss, and together these contributed 12% of the variance. As in the first regression, apnoeic spells occurring in the neonatal period was the most important variable, and the only one to make a significant independent contribution to the variance. Jaundice was the only variable to make a significant addition. Thus, it appears that perinatal illnesses, particularly those known or likely to have caused hypoxia in the newborn period including apnoea, were the most important factors associated with sensory neural hearing loss in this group of very low birthweight infants; jaundice may have had an additive effect.

Discussion

The incidence of sensory neural hearing loss was 9% (10 children) in this group of 111 children of birthweights 1500 g or less. All these children had survived after admission to the neonatal unit of UCH during the years 1966–72, when modern methods of perinatal management were being developed. Among the 10 affected children only 4 (4% of the whole group) were seriously handicapped by hearing impairment; 4 (4%) had moderate losses for which they were able to compensate by wearing hearing aids and receiving extra help within normal schools; and 2 (2%) had hearing which was adequate for perceiving speech without difficulty (Table 4). These figures are the same as those reported by Stennert *et al.* (1977) for a group of children of birthweights 2500 g or less, born 2 years earlier. Reports of other recent follow-up studies of low birthweight infants do not give sufficient data to allow comparison, although Davies and Stewart (1975) reviewing reports of such children suggested that the incidence of moderate to severe hearing impairment among recent very low birthweight survivors may be less than 2%.

Earlier workers reported incidences of about 10–12% of sensory neural hearing loss or moderate to severe deafness in prospective studies of very low birthweight infants (Drillien, 1961; Lubchenco *et al.*, 1963). Other reports gave incidences of 4–15% (Campanelli *et al.*, 1958; McDonald, 1964) for babies of short gestations and very low birthweights, but these figures were either based on selective assessments or were derived from selected groups of deaf children. Thus it is difficult to know if they represent maximum or minimum estimates.

These reports all concerned children who were born at least 20 years ago when little was known or understood about the hazards which low birthweight infants have to overcome in order to survive. Survival rates were low and the incidence of serious handicaps among the survivors was high, suggesting that many had sustained brain damage. What is more, few were nursed in incubators (Douglas and Gear, 1976), and of these, only those born during the 1950s were likely to have been exposed to noise from incubator motors. Incubators in general use before that date usually were heated by manually filled hot water tanks (Hey, 1974). In contrast, all intensive care survivors are likely to have been nursed in potentially noisy motor-driven incubators. In spite of this, the incidence of sensory neural hearing loss among these recent survivors was not greater than among the earlier born infants.

Schulte *et al.* (1977) and Stennert *et al.* (1977) have shown, among low birthweight infants (<2500 g), that 'nonoptimal' perinatal conditions and duration of incubator care both correlate with later hearing defects, but they were unable to separate the two factors. They concluded that noise levels of currently used incubators do not cause sensory neural hearing loss in otherwise healthy preterm infants, regardless of the duration of incubator care, but they were unable to ascertain whether incubator noise may contribute to the excess of hearing deficits noted in infants in whom the perinatal period was 'nonoptimal'.

None of the audiograms of the children with sensory neural hearing loss in this study showed a notch at 4000 Hz which is considered to be characteristic of damage to the cochlea due to long-term noise exposure (Chadwick, 1971). All the audiograms either had a gradual fall of threshold towards the high frequencies, or an abrupt loss at 8000 Hz only. Losses of this kind are generally associated on clinical grounds with anoxic insults or jaundice (Fisch and Osborn, 1954; Fisch, 1955; Fenwick, 1975).

Earlier workers (Johnsen, 1952; McDonald, 1964) suggested that anoxia was probably responsible for the sensory neural hearing loss they observed among low birthweight infants. In our own study, in addition to audiograms typical of this type of insult, or jaundice, perinatal illnesses, particularly those likely to have caused hypoxia in the neonatal period, significantly predicted sensory neural hearing loss; and a serum bilirubin level >170 μmol/1 added significantly to the prediction.

This study shows that sensory neural hearing loss in very low birthweight infants is probably caused by hypoxia in the neonatal period and that jaundice may have an additive effect. We found no evidence to support the suggestion that ambient noise caused by incubator motors contributed to sensory neural hearing loss in these infants all of whom were nursed in commercially available incubators. However, as monitoring devices using noise signals are being used with increasing frequency in the management of such newborn babies, attention should be paid to ambient noise levels to ensure that potentially damaging levels are not exceeded.

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1028 neonatal electrocardiograms

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SUMMARY Electrocardiograms were recorded from 1028 (99·4%) of 1034 consecutively born babies on the 1st or 2nd day of life. Abnormalities of cardiac rhythm or conduction were found in 49 (4·8%) babies. 17 babies had single or multiple premature beats during the recordings, and 7 babies showed sudden increases in R-R interval possibly due to sinoatrial node dysfunction. One baby had pre-excitation, 6 babies had superior QRS axes with clinically normal hearts, and 17 had sinus or junctional bradycardia of <80 beats/min. One baby had an incessant reciprocating tachycardia and subsequently required digoxin for heart failure. Continuous 24-hour ECG monitoring in 25 babies with abnormalities of the screening ECG, and 25 babies without such abnormalities, failed to show any additional tachyarrhythmias or bradyarrhythmias warranting treatment. In view of the uncertain clinical significance of many neonatal arrhythmias and cardiac conduction disorders, more information concerning their natural history and relationship to sudden unexpected death in infancy is needed before recommending that neonatal ECG screening be generally adopted.

Investigation of the neonatal electrocardiogram by both standard and continuous recording techniques has revealed a high incidence of asymptomatic arrhythmias and cardiac conduction disorders in the newborn period (Michaëlsson, 1959; Morgan *et al.*, 1965; Morgan and Guntheroth, 1965; Urbach *et al.*, 1965; Välimäki, 1969, 1971; Välimäki *et al.*, 1974). The importance of arrhythmias as a cause of infant morbidity has been increasingly recognised (Engle and Ehlers, 1973; Ferrer, 1977), while Southall *et al.* (1976, 1977) have drawn attention to potentially life-threatening ECG abnormalities in otherwise healthy newborn infants. These workers have suggested a link between such abnormalities and sudden unexpected death in infancy, and that an ECG performed as part of the routine neonatal examination might identify some babies at risk (Keeton *et al.*, 1977). In the present study we assessed the incidence of arrhythmias and cardiac conduction disorders, together with the feasibility of routine neonatal ECG screening, by performing a 6-lead ECG on a large number of consecutively born infants from a well defined neonatal population.

Methods

Six-lead ECGs (leads I, II, III, aVR, aVl, and aVF; Siemens Cardiostat Electrocardiograph) were performed on 1028 (99·4%) of 1034 babies born consecutively between 1 May and 21 September 1977 at this hospital. During 1977 88% of all deliveries in the Brighton health district (population 300 000) took place in the maternity department of this hospital. The recordings, which included a 10-second rhythm strip (lead II), were performed by one of two residents at the end of the routine neonatal examination on the 1st or 2nd day of life while the baby was resting or feeding in his mother's arms. Some babies were studied in the special care baby unit. Each mother had previously been issued with a typewritten explanatory note. Three babies who died within 7 hours of birth, 2 normal babies, and one baby transferred elsewhere at 2 hours for treatment of a large diaphragmatic hernia were not studied. Babies in whom a heart murmur was heard had a full 12-lead ECG performed.

24-hour ECG tape recordings (Medilog Cassette Recorder, Oxford Electronics Co. Ltd) were performed on 25 babies with abnormalities of the screening ECG, and on a further 25 control babies. These tapes were analysed on a playback system and computerised arrhythmia detector (Pathfinder, Reynolds Medical Electronics Ltd).

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Results

Positive findings are summarised in the Table.

Premature beats. These were found in 17 (1·7%) babies, and were atrial in 12, ventricular in 3, and both atrial and ventricular in 2. They were multiple in 12 cases. 24-hour recordings, performed in 14 babies, showed that premature beats accounted for between 0·4 and 5% of all beats during a 24-hour period. Two babies had 2 consecutive ventricular premature beats, one baby had multifocal ventricular premature beats, and one baby had periods of atrial bigeminy. In 4 babies with atrial premature beats on the initial ECGs, 24-hour recordings showed sudden increases in R–R interval suggesting sinoatrial node dysfunctions. Three of the tapes were normal. No episode of ventricular or supraventricular tachycardia was seen.

Sinoatrial node dysfunction. Many infants showed sinus arrhythmias. Seven showed sudden increases in R–R interval unrelated to respiration and possibly indicating sinoatrial node dysfunctions (Fig. 1). Four of these babies had 24-hour tapes; all showed frequent sudden increases in R–R interval, one showed multiple atrial premature beats, and one showed episodes lasting up to 10 seconds of sinus bradycardia with junctional escape beats at an interval corresponding to a rate of 48 beats/min (Fig. 1).

Pre-excitation. One baby had a short PR interval and delta wave suggesting pre-excitation, and this persisted at follow-up 6 months later. Repeated 24-hour tapes failed to show any clear episodes of supraventricular tachycardia.

Reciprocating tachycardia. One baby, noted to have an irregularity of the fetal heart from the 30th week of gestation and a persistent fetal tachycardia during labour, was found at birth to have a continuous tachycardia of 210 beats/min (Fig. 2). ECG showed inverted P-waves in leads II, III, and aVF, indicating retrograde atrial activation; subsequent recordings showed intermittent brief returns to sinus rhythm. 24-hour tape recordings showed in addition multiple interpolated ventricular premature beats. The P-wave vector and decrease in sinus cycle lengths preceding each initiation of the tachycardia distinguished this abnormality as an 'incessant' or 'permanent' reciprocating tachycardia (Coumel, 1975). It persisted at a rate of 170–210 beats/min, and at age 4 months heart failure necessitated digitalisation. He subsequently returned to sinus rhythm and has remained well.

Table *Positive findings in 1028 neonatal electrocardiograms*

Abnormalities	*No. of babies*
Premature beats (n=17)	
Atrial	12
Ventricular	3
Both	2
Sinoatrial node dysfunction	7
Pre-excitation	1
Reciprocating tachycardia	1
Bradycardia <80 beats/min (n=17)	
Sinus	13
Junctional	4
Superior QRS axis 0 to −120	6
Total	49
Other findings	
Superior QRS axis −120 to −150	15
Variation in P wave shape in lead II	65

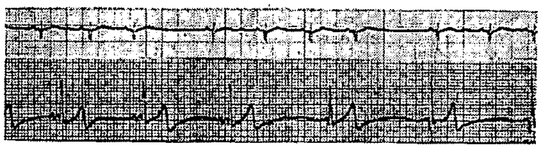

Fig. 1 *Sinoatrial node dysfunction. Upper trace: lead II showing sudden increase in R–R interval. This is preceded by a progressive decrease in P–P interval suggesting 2nd degree (Wenckebach) sinoatrial block. Lower trace: 24-hour tape of same infant showing sinus bradycardia with junctional escape beats at an interval corresponding to a rate of 48 beats/min.*

Sinus and junctional bradycardia. Heart rates of <80 beats/min were seen in 17 (1·7%) babies, the

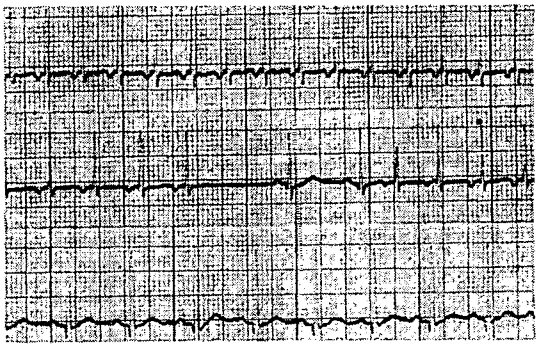

Fig. 2 *Incessant or permanent reciprocating tachycardia. Upper trace: lead II on day 1 showing tachycardia of 210 beats/min, the inverted P–waves indicating retrograde atrial activation. Middle trace: day 2 showing brief return to sinus rhythm followed by recurrence of the tachycardia, the premature impulse showing a slightly altered QRS configuration due to aberrant conduction. Lower trace: sinus rhythm after digitalisation at age 4 months.*

slowest rate being 60. The bradycardia was sinus in 13 cases, and junctional in 4. 24-hour tapes, performed in 5 of these babies, did not show any bradycardias of <60 beats/min, nor did they reveal additional arrhythmias.

Superior QRS axis. The frontal plane QRS axis was 0 to −120 in 6 babies, none of whom had any clinical evidence of structural heart disease. Of 4 of these babies followed up, only one had a persistently superior axis at age 3 months.

Other screening ECG findings. The QRS axis was between −120 and −150 in 15 babies, all of whom had clinically normal hearts. Variation in P–wave shape in lead II was observed in 65 (6·4%) babies (Fig. 3) and was associated with the occurrence of atrial premature beats ($\chi^2 = 45{\cdot}7$, $P < 0{\cdot}001$).

Control 24-hour tapes. These were performed in 25 babies whose screening ECGs had been normal. Sinus rates varied between 60 and 240 beats/min. Two babies showed occasional atrial premature beats, and one baby had 2 isolated ventricular premature beats. Two babies had sudden increases in R–R interval, suggesting sinoatrial node dysfunctions. One preterm baby had repeated episodes of sinus bradycardia at a rate of 50 beats/min lasting up to 10 seconds. No sustained tachyarrhythmias or bradyarrhythmias were seen.

No significant association was found between any ECG abnormality and preterm delivery, birthweight, birth asphyxia, or neonatal respiratory illness. Except for one baby who developed heart failure due to reciprocating tachycardia (Fig. 2), there was no clinical disturbance in any baby with an abnormal ECG, and none had any evidence of structural congenital heart disease.

One baby in the study died suddenly and unexpectedly at home at age 6 months. She had been born at 35 weeks' gestation, and the screening ECG, apart from showing tall P-waves in lead II suggesting right atrial hypertrophy, was normal. No cause of death was found at necropsy and detailed histology of the cardiac conducting tissue (Dr R. Anderson, Brompton Hospital) was normal.

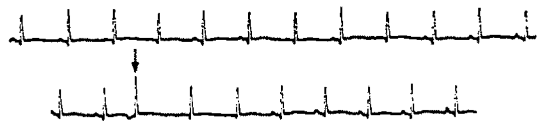

Fig. 3 *Variation in P–wave shape in lead II. Note suppression of sinoatrial node activity after atrial premature beat (arrowed).*

Discussion

Although the present study confirms that arrhythmias and cardiac conduction disorders may be detected by routine ECG screening in otherwise healthy newborn infants, the relationship of these abnormalities to subsequent morbidity remains uncertain. Both premature beats and pre-excitation may occur as transient phenomena in early infancy (Friedman *et al.*, 1969; Välimäki, 1971), but may also be associated with tachyarrhythmias (Moene and Roos, 1973; Silver *et al.*, 1973; Southall *et al.*, 1977), although in the present study we were unable to document any such association using either standard ECGs or 24-hour recordings. We also failed to detect any tachyarrhythmias or bradyarrhythmias requiring treatment in 25 control babies studied by 24-hour taped ECGs. Although the range of ECG abnormalities was similar, the incidence of potentially serious arrhythmias was therefore low compared with that found by Southall *et al.* (1976, 1977). One baby, however, developed heart failure due to an incessant reciprocating tachycardia (Fig. 2), an arrhythmia previously described in infancy and shown by intracardiac electrophysiological studies to be due to a re-entry mechanism in the region of the atrioventricular node and upper His bundle (Coumel, 1975). This arrhythmia was detected antenatally, underlining the importance of considering the possibility of fetal arrhythmia when persistent fetal tachycardia or heart irregularity is noted during pregnancy or labour.

Supraventricular tachycardia is a well documented cause of heart failure in the perinatal period (Radford *et al.*, 1976), and has also been found in some cases of 'near miss' sudden unexpected death in infancy (Keeton *et al.*, 1977). The significance of bradyarrhythmias is less certain, and in many cases occurs secondarily to apnoea (Girling, 1972) or increase in vagal tone (Cordero and Hon, 1971), junctional escape rhythms reflecting the relatively high intrinsic firing rates of the subsidiary pacemaker tissues in this age group. Sinus arrhythmia and sudden changes in heart rate are common in the newborn, especially when preterm, and may reflect autonomic immaturity (Lipton *et al.*, 1965; Church *et al.*, 1967). The abrupt increases in R-R interval noted in babies in the present study may have a similar aetiology, but might alternatively be a manifestation of dysfunction of the sinoatrial node, especially in those cases associated with episodes of sinus or junctional bradycardia (Fig. 1). Although sinoatrial node dysfunction has recently been recognised as a cause of syncopal attacks in older children even in the absence of structural heart disease (Scott *et al.*, 1976), its significance in the newborn period is uncertain. Variation in P-wave shape (Fig. 3) has previously been ascribed in adults to variability in the site of formation and subsequent atrial conduction of the sinoatrial node impulse (Brody *et al.*, 1967). This phenomenon in the newborn, together with the occurrence of sinoatrial node dysfunction and the tachycardia-bradycardia syndrome (Southall *et al.*, 1977), supports the concept of continuing functional maturation of the sinoatrial node in early postnatal life. Confirmation of this hypothesis awaits more detailed study of sinoatrial node function in this age group.

A superior QRS axis is often associated with structural congenital heart disease, most frequently an atrioventricular canal or ventricular septal defect in the acyanotic infant (Shinebourne *et al.*, 1974). Only one baby in the present study had a persistently superior QRS axis which, in the absence of any clinical evidence of structural defects, probably represents isolated left anterior hemiblock.

Sudden unexpected death in infancy represents a spectrum of diseases and social situations, and Emery (1977) considers that only a few, perhaps 10%, are likely to be due to cardiac arrhythmias. From this figure, it has been estimated that more than 40 000 neonates would have to be screened before a significant association could be shown (D. Southall, personal communication). In addition, it is not certain that an infant who dies suddenly from cardiac arrhythmia will necessarily have any abnormality detected by a screening ECG in the neonatal period. It nevertheless seems reasonable to investigate cases of 'near miss' sudden unexpected deaths with a standard ECG and, if possible, with 24-hour ECG combined with respiratory tape monitoring, the latter in order to assess the incidence and timing of apnoea in babies with bradyarrhythmias. The provision of *routine* neonatal ECG screening, however, together with 24-hour tape recording and analysis, gave our neonatal department a sizeable additional work load and also generated some maternal anxiety. Until there is more information concerning the natural history of neonatal ECG abnormalities and their relationship to sudden unexpected death in infancy, it is premature to recommend the general adoption of neonatal ECG screening.

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Sinusoidal heart rate rhythms in severe neonatal hypoxia

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SUMMARY Sinusoidal heart rate traces were detected in 8 patients, 6 of whom died; the 2 survivors showed evidence of gross cerebral damage. It is felt that the origin of the sinusoidal curve is probably central and reflects loss of central control of heart rate.

Continuous monitoring of the fetal heart rate through labour has led to the detection of abnormal heart rate patterns indicative of fetal distress. One significant pattern detected by Baskett and Ko (1974) and Manseau *et al.* (1972) was the sinusoidal heart rate pattern, characterised by slow regular wave forms in the fetal heart rate. This pattern in the neonatal period was also described by Ekert and Schenk (1974). In all reports the appearance of this pattern was associated with a poor prognosis. We wish to report our observations on sinusoidal heart rate patterns seen in 8 infants in a one-year period in two special care baby units in Belfast.

Patients and methods

During a period of one year all ill newborn infants receiving intensive care in our units in Belfast were monitored using cardiorespirographs (Corometrics 512 and Hewlett-Packard Cardio-Respiratory Monitor 78250A). These monitors detect successive R-waves on the electrocardiograph and give an instantaneous heart rate, both as a digital read-out and on a paper trace. The respiratory rate and amplitude are detected, by an impedance method, by two electrodes placed laterally on the chest wall.

During the period under review 130 infants were monitored. The infants suffered from a variety of conditions including idiopathic respiratory distress syndrome (IRDS), severe congenital heart disease, rhesus haemolytic disease, and apnoeic spells of prematurity. The clinical data of the 8 patients with sinusoidal heart rate traces are given below.

Case 1. A baby boy delivered by caesarean section in a peripheral hospital at 43 weeks' gestation with a birthweight of 4600 g. Caesarean section was performed because of delay in labour which had lasted 36 hours. Meconium-stained liquor had been passed and fetal bradycardia had occurred intermittently in the 24 hours before delivery. The Apgar score was 2 at five minutes and spontaneous respirations were not attained until age 10 minutes. The infant then developed a series of apnoeic spells and was transferred at age 6 hours. On admission the infant was hypotonic and had periodic apnoeic spells. Six hours later convulsions developed which were then treated with intravenous diazepam. In spite of this the infant developed further convulsions and became increasingly hypertonic and died at age 3½ days. Necropsy showed cerebral softening and oedema but with no haemorrhage or significant abnormalities of other organs.

Case 2. A baby boy with a birthweight of 3600 g, delivered by forceps in a peripheral hospital. The Apgar score was 3 at five minutes and regular respirations were not established until 45 minutes despite active resuscitation. The infant was transferred and admitted to our unit at age 11 hours. At that time he was shocked, cyanosed, and hypoventilating. He was hypotonic and developed increasingly frequent apnoeic spells and died at age 2 days. Necropsy showed cerebral oedema and also subarachnoid, subdural, and pulmonary haemorrhage.

Case 3. A baby girl weighing 3500 g. Delivery was by Kielland's forceps for occipito-posterior position and abruptio placenta at term. Apgar scores were 2 and 4 at two and five minutes respectively. Active resuscitation was carried out but spontaneous

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respirations were not attained until 30 minutes. During the next 24 hours the baby became hypertonic and developed convulsions associated with bradycardia, apnoea, and cyanotic attacks. CSF was evenly blood stained. Spontaneous recovery occurred and the infant survived but suffers from microcephaly, spastic quadriplegia, salaam attacks, and gross developmental delay.

Case 4. A baby boy weighing 2900 g at term by normal delivery. Fetal distress had occurred during labour and the infant's Apgar scores were 4 and 2 at two and five minutes. During the first 4 days of life he was deeply unconscious and suffered from convulsive episodes and occasional apnoeic spells. Tone was variable, being initially hypotonic and then hypertonic. The infant survived but is now microcephalic with salaam spasms and pronounced hypotonia. There is also gross developmental delay.

Case 5. A baby boy born at 35 weeks' gestation by normal delivery, with a birthweight of 2700 g after spontaneous onset of preterm labour in a peripheral hospital. The infant's condition was satisfactory at birth but he then developed IRDS which was confirmed by chest *x*-ray. He was therefore transferred to one of our units at 20 hours of age. On examination he was severely ill, and cyanosed in 100% oxygen with an arterial PO_2 of 17. The pH was 6·89 and Pco_2 was 132. The infant was intubated and received intermittent positive pressure ventilation (IPPV), but died one hour later aged 21 hours. Necropsy showed evidence of pronounced pulmonary atelectasis and also subarachnoid haemorrhage.

Case 6. A baby girl born by normal delivery at 29 weeks' gestation, birthweight 1300 g, after spontaneous onset of labour. Apgar scores were 1 at five and 2 at ten minutes. In spite of active resuscitation the infant remained very ill with intermittent apnoeic spells and convulsions. CSF was evenly blood stained and the fontanelles were distended and tense, suggesting intracranial haemorrhage. The infant developed bronchopneumonia and died aged 4 days. Unfortunately consent for necropsy could not be obtained.

Case 7. A baby girl born by assisted breech delivery at 29 weeks' gestation with a weight of 1130 g after spontaneous onset of preterm labour. Apgar score was 4 at two minutes and the baby rapidly developed respiratory distress. On admission to the special care baby unit she was noted to be anaemic with a haematocrit of 40. The infant was treated with IPPV, blood transfusion, and correction of acidosis, but she failed to respond to treatment and died aged 6 hours 20 minutes. Necropsy showed a small intraventricular haemorrhage and pronounced pulmonary atelectasis.

Case 8. A baby boy delivered at 28 weeks' gestation after antepartum haemorrhage and breech delivery. The birthweight was 1080 g, Apgar score was 1 at two minutes. Spontaneous respirations were not established and the baby was treated with IPPV; however, he failed to respond to treatment and died aged 18 hours. Necropsy showed pronounced pulmonary atelectasis, a small pulmonary haemorrhage, and subarachnoid haemorrhage.

These clinical features together with a description of the sinusoidal patterns are shown in the Table.

All 8 infants demonstrated a sinusoidal heart rate. Cases 4 and 8 (Figs 1 and 2) are shown as examples. The frequency of the sinusoidal curve varied in the infants from once every 30 seconds to once every

Table *Clinical features and sinusoidal heart rate patterns in 8 infants*

Case	*Weight (g)*	*Diagnosis*	*Sinusoidal pattern*			*Outcome*
			Duration	*Frequency (min)*	*Rate/min*	
1	4600	Asphyxia	3 h	3½	110–130	Died 3½ days. Necropsy: cerebral oedema and softening
2	3600	Asphyxia	40 min	2½	120–180	Died 2 days. Necropsy: subarachnoid and subdural haemorrhage
3	3500	Asphyxia	4 h	1	140–150	Lived. Microcephaly, epilepsy, and spastic quadriplegia
4	2900	Asphyxia	48 h	1½	90–120	Lived. Microcephaly, epilepsy, and hypotonia
5	2740	IRDS	8 min	1	110–150	Died 21 hours. Necropsy: atelectasis, subarachnoid haemorrhage
6	1300	Asphyxia, bronchopneumonia	12 h	½	130–150	Died 4 days. No necropsy. Intraventricular haemorrhage and bronchopneumonia
7	1130	Asphyxia, IRDS	35 min	1	60–120	Died 6 hours. Necropsy: atelectasis, intraventricular haemorrhage
8	1080	Asphyxia, IRDS	8 min	1¼	105–140	Died 18 hours. Necropsy: atelectasis, subarachnoid haemorrhage

3½ minutes and the amplitude from 10 to 60 beats/min. None of the remaining 122 infants who were monitored showed sinusoidal heart rate rhythms. 14 of these infants died, of whom 4 showed evidence of cerebral disease at necropsy but had not exhibited the sinusoidal curve patterns during life. The remaining infants died of extreme prematurity, with or without IRDS, or from congenital malformations. Of the 108 babies who were monitored and survived and who did not show sinusoidal heart rate patterns, none to date has shown evidence of neurological impairment although the follow-up period has been short, most of these infants still being under one year.

Discussion

Sinusoidal heart rate rhythms can clearly be distinguished from other heart rate patterns seen in the neonatal period as Figs 3 and 4 clearly show. Previous authors have noted that this pattern is associated with a grave prognosis, and all 8

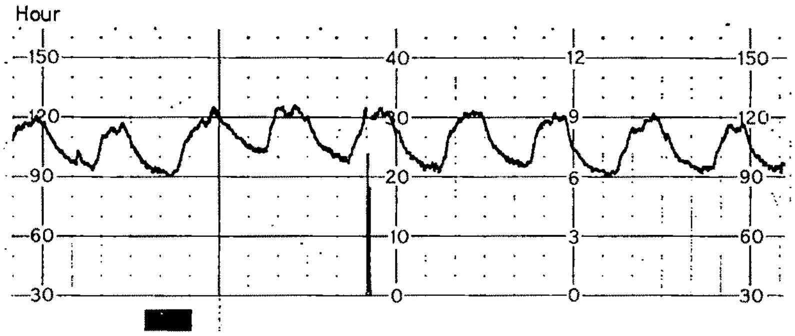

Fig. 1 *Vertical axis heart rate. Horizontally each major dark line represents a 6 min-interval.*

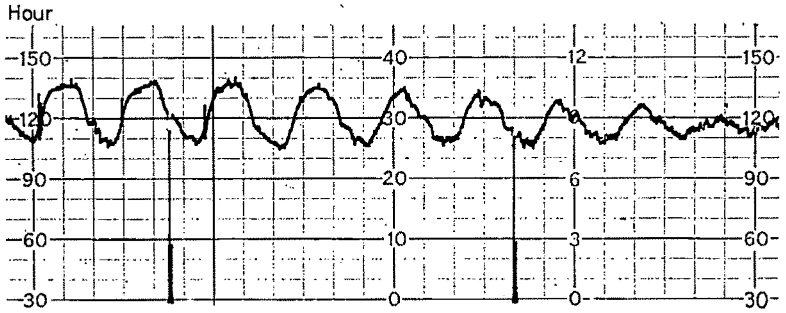

Fig. 2 *Vertical axis heart rate. Horizontally each major dark line represents a 6 min-interval.*

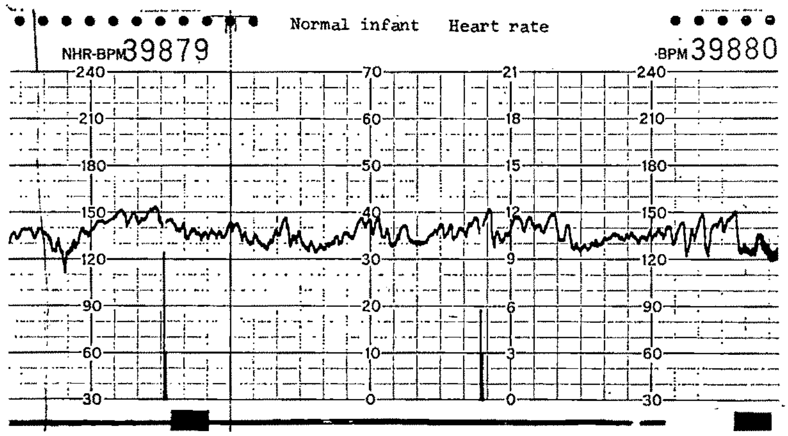

Fig. 3 *Normal infant, normal heart rate pattern.*

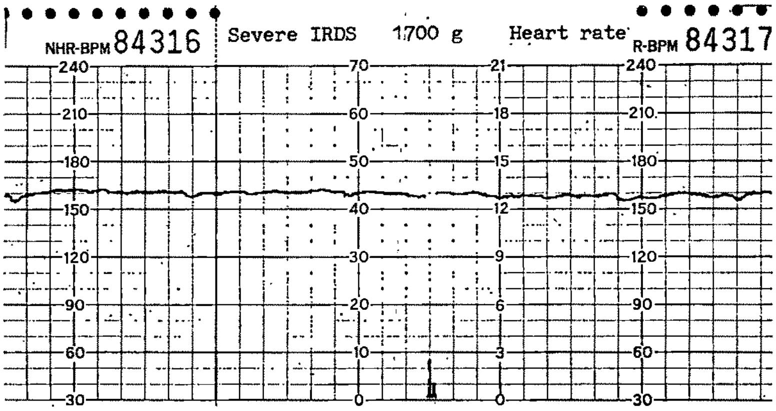

Fig. 4 *Heart rate 'flat'. Heart rate trace in an infant with severe IRDS.*

infants in whom we have seen this pattern have either died or have had gross residual cerebral damage. Other heart rate abnormalities, such as decreased heart rate variation, have been seen in children with brain damage and it is claimed that it may be considered a clinical criterion of brain death (Kero *et al.*, 1978). However, it must be stressed that the total observation of the sinusoidal heart rate pattern is extremely limited and many further observations would be needed to confirm its prognostic significance.

The origin of the sinusoidal curve is in some doubt. Heart rate deceleration may occur in response to a primary respiratory event as we would expect in the current apnoeic episodes. Valbona *et al.* (1965) studied adults with decerebrate states and described similar patterns with prominent waves of acceleration of heart rate rhythm followed by rebound deceleration. These waves coincided with each deep breath or with the onset of periodic breathing. Guilleminault *et al.* (1977) described cardiac arrhythmias in adults with apnoeic spells and severe CNS disease. In several of our patients the sinusoidal wave pattern was associated with recurrent regular apnoeic spells. However, in our cases there was no fixed relationship between the occurrence of apnoea and cardiac deceleration, as 3 of our 8 patients were receiving IPPV at the time when the sinusoidal heart rate pattern was seen. We feel that in these 3 cases at least, the sinusoidal heart rate pattern is unlikely to be a primary respiratory event and is more probably central in origin and may reflect a lack of central control of cardiac rhythm.

Sinusoidal patterns could also possibly be a primary cardiac phenomenon reflecting either conduction defects or a diseased myocardium. Cardiac arrhythmias have been reported in fetuses and infants during hypoxic stress but unfortunately in none of our patients did we obtain either direct electrocardiographic traces or cardiac enzyme studies. These patterns appear to have a grave prognosis, but as there is little experience we would urge caution in their interpretation, and we hope that there will be many further observations before any conclusions are made and the patients treated accordingly.

We thank all the junior medical staff and nursing staff for their careful record keeping and assistance in the collection of these records. J.J. is in receipt of a fellowship from DHSS, NI.

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Breath hydrogen test for detecting lactose malabsorption in infants and children

Prevalence of lactose malabsorption in Japanese children and adults

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SUMMARY The breath hydrogen test (BHT) was adapted for use in young infants and children. The diagnostic criterion of sugar malabsorption in the BHT was determined by oral administration of 0·5 g/kg of unabsorbable sugar (lactulose) to 21 healthy infants and children. A maximum increase in breath hydrogen $>0{\cdot}05$ ml/min per m^2 was observed in all subjects. A good correlation between results by the BHT and by the ordinary lactose tolerance test was obtained after oral administration of 2 g/kg lactose to 21 healthy infants and children, 2 congenital lactase-deficient infants, and 7 adults.

Using this test, 80 healthy Japanese infants and children (aged between one month and 15 years) and 18 adults were examined for lactose malabsorption after a dose of 1 g/kg lactose. All infants and children under 2-years old absorbed lactose completely. The incidence of lactose malabsorption was 30% in 3-year, 36% in 4-year, 58% in 5-year, and 86% in 6-year-old children, 85% in schoolchildren, and 89% in adults. Thus the incidence of lactase deficiency gradually increases with age from 3 years, and about 90% of all normal Japanese adults are lactase-deficient.

At birth, humans have abundant lactase activity in the small intestine but, in most ethnic groups, there is a pronounced decrease in lactase activity during early childhood (Huang and Gayless, 1967; Johnson *et al.*, 1977). The definitive diagnosis of lactase deficiency requires the collection of biopsy specimens from the small intestine and demonstration of decreased lactase activity therein. Attempts have therefore been made to develop indirect methods for detecting lactase deficiency. Tolerance tests, although commonly used for this purpose, are influenced by many factors—such as, the rate of gastric emptying and intermediary glucose metabolism. In addition, these tests need a large amount of lactose and therefore give no information on the ability of the intestine to absorb smaller, more physiological quantities. Moreover, the results are often unreliable (Krasilnikoff *et al.*, 1975).

Recently, many investigators have shown that the breath hydrogen test (BHT) (change in the concentration in the breath of hydrogen formed by bacterial metabolism of unabsorbed lactose in the colon) is a simple, accurate, and sensitive indirect test for lactase deficiency in adults (Levitt, 1969; Bond and Levitt, 1972; Newcomer *et al.*, 1975). There have been only a few reports of this test on children under 5 years (Maffei *et al.*, 1977).

We report the application of this test in children, of from one month old upwards, and in adults to determine the incidence and age of onset of lactase deficiency in Japanese children.

Subjects and methods

Subjects. Hydrogen excretion was studied in 80 healthy children (between one month and 15 years old), 2 infants with congenital lactase deficiency (diagnosed by per-oral intestinal biopsy), and 18 normal adults (between 20 and 50 years old). Of the

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80 children, 19 were infants (between one and 12 months old), 42 were preschool children (between 2 and 6 years old), and 19 were schoolchildren (between 7 and 15 years old). Informed consent was obtained from the adults and the children's parents.

Methods. The ability of the colonic flora of infants to produce H_2 during lactose fermentation was studied using faecal homogenates as described by Bond and Levitt (1972). Fresh faecal specimens (2 g) from 50 infants (15 newborn infants feeding with breast milk, 6 newborn babies with formula, 25 infants with formula, and 4 children) were homogenised in 4 ml of 0·10 mol/l phosphate-buffered saline (pH 7·0). All infants examined were healthy and not receiving treatment with antibiotics. The homogenates were placed in a series of 10 ml test-tubes and 1 ml 1·25% (mass/vol.) lactose solution was added to each. The tubes were mixed, sealed with rubber stoppers, and placed in a water bath at 37°C. A needle attached to a 50-ml syringe was inserted through the rubber stopper. After one hour, the tubes were vigorously stirred, and the gas in each tube was displaced into the syringe by injecting water into the test-tube through a second syringe. The concentration of H_2 was determined by gas chromatography.

Respiratory H_2 excretion

The subjects were starved overnight, and then the rate of respiratory H_2 excretion was determined at 0, 1, 2, 3, and 4 hours after carbohydrate loading by analysis of 3-min samples of expired air. As the H_2 concentration of expired air was often too low to measure accurately, a rebreathing technique, a modification of the method of Levitt (1969), was used to concentrate the breath H_2. An infant circle, which is normally used for anaesthesia of infants, was used as the collecting system. The apparatus contains a flutter valve, CO_2 absorbent, 3-litre neoprene bag, and a 2nd flutter valve. Hydrogen was considered to be evenly distributed in a volume of gas equal to that present in the collecting system, plus the residual lung volume of the subject (estimated from a nomogram for normal Japanese children (Nakajima, 1967)). The volume of the infant circle (except for bag volume) was measured by the dilution method and the average value in 20 determinations was 980 ± 20 ml. After the collection period, the bag volume was measured. The total volume was taken as 980 ml, plus the bag volume, plus the residual lung volume. This total volume multiplied by the concentration of H_2 in the collecting system was defined as the volume of H_2 excreted during a 3-min period. The system was flushed with O_2 between collections. With infants of <6 months old, expired air was collected by a modification of the to-and-fro rebreathing method of Krauss and Auld (1970). For this, a neoprene rubber bag of 1·5 litres was used, and the volume of the collecting system was nearly equal to the bag volume, because the dead space was very small (about 20 ml).

As soon as possible after collection, samples were analysed for H_2 by gas chromatography using a thermal conductivity detector (Shimazu Seisakusho, Ltd, Model GC-4B, Kyoto, Japan). A 2-ml sample of gas was introduced through a gas sample valve into a stainless steel column, 2 m × 0·4 cm (inside diameter), packed with 80-mesh molecular sieve 5A. Oven temperature was 75°C. N_2 (flow rate 20 ml/min) was used as carrier gas. The smallest detectable amount of H_2 was 5 ppm (0·05 ml in 10 litres), corresponding to the excretion of 0·0025 ml/min (as the minimum volume of the collecting system was about 1·5 litres). A single H_2 determination took only a few minutes.

Plasma glucose

Venous blood samples were obtained at 0, 30, 60, 90, and 120 min after glucose and lactose loading. Plasma glucose was determined by the glucose oxidase method.

Results

Out of faecal specimens from the 50 infants, 48 samples produced considerable hydrogen. The mean fasting breath H_2 output of 80 subjects was $0{\cdot}027 \pm 0{\cdot}016$ ml (1 SD)/min per m^2 (range 0·000 to 0·068). Usually the peak level for H_2 concentration occurred 2 or 3 hours after oral sugar administration. The fasting levels were subtracted from the peak levels, and the results were expressed as the increase above the fasting level. The reproducibility of the technique for collecting breath H_2 was studied in 4 infants and 4 children during a lactulose (unabsorbable sugar) loading test by comparing their rates of breath H_2 excretion during 2 consecutive 3-min periods ($n = 16$). The mean difference between the 2 determinations was 10·7% with a range of 1·3 to 15% (range of H_2 concentration was 27 to 167 ppm). The change in breath H_2 excretion in healthy subjects (7 infants, 7 preschool children, and 7 schoolchildren) after oral ingestion of lactulose or glucose (an absorbable sugar) is shown in Fig. 1. Breath H_2 excretion increased markedly (>0·05 ml/min per m^2) in each of the 21 subjects after ingestion of 0·5 g/kg lactulose (10% solution), but did not increase above the basal level after ingestion of 2 g/kg glucose. In fact, in the subjects given glucose, breath H_2 excretion decreased gradually.

In these 21 subjects, 2 congenital lactase-deficient

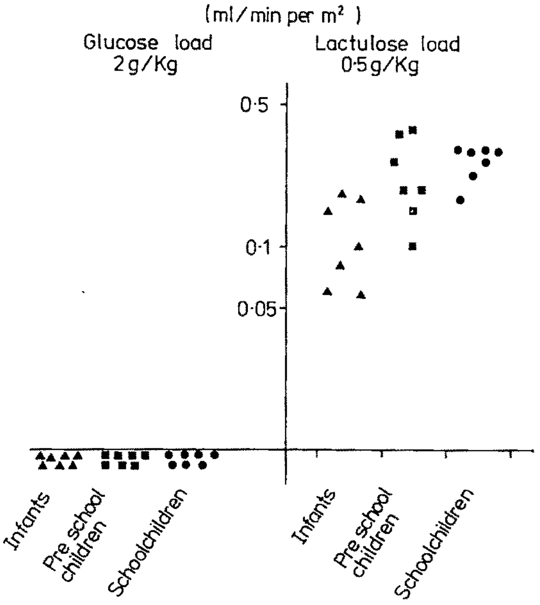

Fig. 1 *Maximum increase of breath H_2 excretion after oral administration of glucose (2 g/kg) and lactulose (0·5 g/kg), in children of various ages. Increase in H_2 is expressed as ml/min per m^2 body surface area.*

infants, and 7 normal adults, we compared the relationship between the maximum increase of breath hydrogen excretion and the maximum increase of the blood sugar level after oral ingestion of 2 g/kg (maximum 50 g) lactose (10% solution).

Fig. 2 shows the maximum increase in blood sugar in each subject plotted against the maximum increase in breath H_2 excretion. Subjects who had a normal tolerance test—that is, >20 mg/100 ml (1·1 mmol/l) increase in blood sugar—showed less than 0·05 ml/min per m² increase in H_2 excretion, and no clinical response. On the other hand, those who had <20 mg/100 ml increase in blood sugar showed an increase in breath H_2 excretion of >0·05 ml/min per m² and some of these subjects developed clinical symptoms—such as diarrhoea, cramp, bloating, flatulence, or borborygmi—particularly the 6 adults and 2 congenital lactase-deficient infants.

To examine the effect of age on H_2 excretion, we carried out the breath hydrogen test after oral ingestion of 1 g/kg lactose (10% solution) in 80 healthy infants and children and 18 adults. The maximum increase in breath H_2 is plotted against age in Fig. 3. All the infants and children of under 2 years could absorb lactose completely, but 30% of the 3-year-old children showed an increase of breath H_2 >0·05 ml/min per m², indicating lactose malabsorption. The incidence of lactose malabsorption was 36% in 4-year, 58% in 5-year, 86% in 6-year-old children, 85% in schoolchildren, and 89% in adults.

Discussion

A simple, reliable, and noninvasive test of sugar absorption is required for diagnosis and for studying malabsorption syndromes and adult-type lactose malabsorption in children. The technique of intermittent breath sampling for analysis of breath H_2 was developed by Levitt (1969) and is now established as the most accurate indirect test of disaccharide intolerance in adults. However, this test had not been applied to infants and children with a total collection method, so we adapted it for use on children.

We first tested whether the intestine of children contains the H_2-producing bacteria that are essential

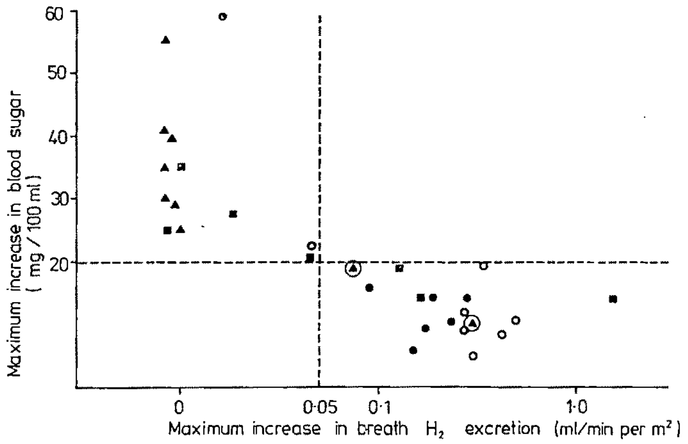

Fig. 2 *Relationship of maximum increase in breath H_2 excretion with maximum increase in blood sugar level after ingestion of 2 g/kg lactose (▲ infants, ■ preschool children, ● schoolchildren, Ⓐ congenital lactase-deficient infants, o adults).*

Conversion : traditional units to SI—blood glucose 1 mg/100 ml ≈ 0·0555 mmol/l.

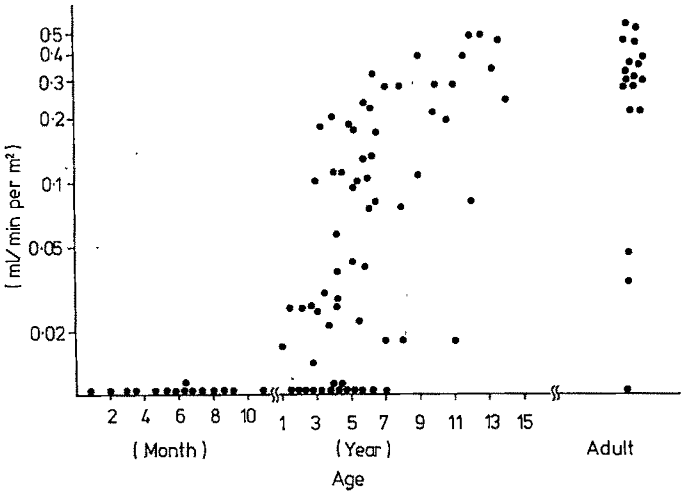

Fig. 3 *Maximum increase in breath H_2 excretion after ingestion of 1 g/kg lactose (maximum 50 g) at various ages.*

for application of this test. *In vitro* tests on the faeces of 50 infants of various ages showed that almost all (96%) infants have colonic flora that produce H_2. Thus the breath H_2 test may be applied to infants. The breath H_2 collecting technique used by Newcomer *et al.* (1977) is an accurate method for older children, but the apparatus is too big and complex for children under 5 years and the rebreathing time too long, so that accuracy may be poor. The methods of end-expiratory breath H_2 sampling reported by Maffei *et al.* (1977) and Caskey *et al.* (1977) can give good information, but it is less precise than the total collection method (Metz *et al.*, 1976). However, as the total volume of collecting system is small in our method, and a detectable increase in concentration of H_2 gas in the system can be obtained in 3 minutes, we achieved satisfactorily accurate quantitative sampling of breath H_2. To reduce the total volume of the collecting system for infants under 6 months, the expiratory air was sampled using a to-and-fro rebreathing system. Our technique for collecting breath H_2 gave reproducible results, even with children under 5 years.

According to Newcomer and McGill (1977), 25 g (0·3–0·5 g/kg) of unabsorbed sugar may be enough to provide a distinct increase in breath H_2 in adults. On the other hand, we found that some patients began to develop clinical symptoms—such as diarrhoea, borborygmi, and abdominal distention—after administration of >0·5 g/kg lactulose, suggesting that the presence of more than 0·5 g/kg of unabsorbed sugar in the large intestine may cause clinical symptoms. So we tentatively made the presence of 0·5 g/kg unabsorbed sugar in the large intestine a diagnostic criterion of sugar malabsorption. For example, if an infant of 10 kg was given 10 g lactose, half of which was not absorbed (absorption rate 50%), a certain amount of H_2 would be produced. On the other hand, if a man of 50 kg was given 50 g lactose, and 5 g lactose was not absorbed (absorption rate 90%), H_2 excretion derived from unabsorbed sugar may be the same, since the amount of breath H_2 may reflect the absolute amount of unabsorbed sugar (Bond and Levitt, 1976). We thus thought it reasonable to establish a criterion of sugar malabsorption in BHT, by dividing H_2 excretion/min by body surface area. We first attempted to demonstrate an appreciable maximum increase in breath H_2 after oral administration of 0·5 g/kg lactulose to healthy infants and children of various ages. As shown in Fig. 1, even in infants, a definite increase of breath H_2 excretion (>0·05 ml/min per m²) was detected after administration of 0·5 g/kg of unabsorbable sugar (lactulose). On the other hand, when an absorbable sugar (glucose) was administered (2 g/kg) to the same subjects, no increase of breath H_2 was observed in any age group. These findings show that our method is reliable and accurate for evaluating sugar absorption. Moreover, as Fig. 2 shows, there was good correlation between the results of the ordinary lactose loading test and the results of the breath H_2 test.

We then carried out the breath H_2 test after oral ingestion of 1 g/kg lactose to determine the incidence of lactose malabsorption. We chose this dose of lactose for the following reasons: (1) it is more physiological than that ordinarily used (2 g/kg), because uptake of lactose, at one time, from the diet does not usually exceed 1 g/kg (Hegsted, 1976; Newcomer *et al.*, 1978); (2) the absorption of less than half the administered lactose may be reasonably defined as lactose malabsorption. Thus, judging from the fermentation of various sugars (Bond and Levitt, 1972) and our results with lactulose loading, if half the lactose is not absorbed after a load of 1 g/kg, there should be an increase of breath hydrogen $>0 \cdot 05$ ml/min per m^2.

Our results showed that all infants and children under 2 years could absorb lactose completely. Lactase deficiency seems to appear at 3 years and it gradually increases with age; 85% of the children of over 6 years, and about the same percentage of adults, showed lactose malabsorption.

There have only been two previous reports on the age of onset and prevalence of lactose intolerance in Japanese people. Shibuya *et al.* (1970) reported a somewhat earlier age of onset of lactose intolerance and 100% incidence of lactose intolerance after 8 years by using the ordinary lactose tolerance test. As the ordinary lactose tolerance test gives about 20% false-positive results (Krasilnikoff *et al.*, 1975), their results are not essentially different from ours. Naito *et al.* (1973) investigated the effect of age on lactase activity, and found an adult-type pattern of lactase activity in children of over 6 years.

There are two reports of studies on American Indians using breath H_2 analysis. Newcomer *et al.* (1977) observed lactase deficiency by age 5, but they did not obtain satisfactory results on younger children; Caskey *et al.* (1977) made similar studies but their results are not comparable with ours because of the difference in method.

The breath H_2 test has many advantages (Metz *et al.*, 1976; Fernandes *et al.*, 1978) and should have wide application for elucidating problems of sugar absorption in children.

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Giant exomphalos—conservative or operative treatment?

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SUMMARY The rate of survival for infants with intact giant exomphalos has much improved during the last 20 years; this is partly due to better respiratory and nutritional support. The use of a staged operative closure using a sialon prosthesis has been advocated for 12 years, but our data do not show this to be superior to nonoperative management.

Children with intact exomphalos pose considerable problems in management. The first question is whether an operative or a nonoperative method should be used when simple closure is not possible either because of the size of the defect or because of the contents of the sac.

Nonoperative treatment using drying agents—such as mercurochrome or alcohol—to encourage cicatrisation, first advocated in 1899 by Ahlfeld, still has support, and if it is successfully used the child is left with a soundly healed abdominal wall or one that requires little subsequent surgery (Grob, 1963; Soave, 1963).

The skin mobilisation method of surgical treatment (Olshaussen, 1887; Gross, 1948) usually leaves an enormous hernia and there are significant technical problems in later repair of the abdominal wall. Subsequent surgery for this defect carries a mortality rate of 27% (Shuster, 1967).

Survival rates of patients with large exomphalos have been poor; in Melbourne between 1952 and 1962 the mortality rate was 75% for infants with defects of 5 cm or more across (Jones, 1963).

The arrival of a new concept in treatment, that of staged reduction by exterior pressure applied with a sac sutured to the edge of the defect (Shuster, 1967) was greeted by many surgeons as the answer to this problem. The aim of this treatment was to reduce the defect as quickly as possible with early discharge of the patient from hospital. However, our experience with this method of treatment has not been entirely satisfactory, so we were prompted to review our patients.

Materials and methods

Between 1967 and 1977, 87 patients were admitted to the neonatal unit of this hospital with intact exomphalos. 17 of these had defects measuring >5 cm diameter at the base, and they were retrospectively reviewed. Primary closure of muscle and skin was possible in 3 of them, 6 were selected according to the preference of the responsible surgeon for treatment by the Shuster technique using a sialon pouch, and 8 were similarly chosen for nonoperative treatment.

Results

There were 3 patients in whom primary closure was possible with a survival rate of 100%. One child has had two exchange transfusions for jaundice and at review had a pronounced hearing loss. There were no other medical or surgical problems in this group and their stay in hospital was about 3 weeks.

Two of the 6 patients treated with sialon prosthesis died. None had any other major malformation and both deaths were in the first 2 weeks of life. The cause of death was Gram-negative sepsis while on appropriate chemotherapy. Two of the survivors needed major reconstructive surgery of the abdominal wall and this was completed successfully. The patients treated by this staged repair stayed in hospital for between 4 and 7 weeks, but we noted that during the period that the prosthesis was *in situ*, no patient could be successfully established on alimentary feeding, so total parenteral nutrition was undertaken routinely in this group.

Eight patients were given conservative treatment and 3 of them died. Two deaths were due to associated malformations; one death at 24 hours was due

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to Potter's syndrome and the other, from cardiac failure at age one week, was due to Fallot's tetralogy. Both diagnoses were confirmed at necropsy. In the remaining 6 patients the intact sac was painted with 2% aqueous mercurochrome. There was one death of a child in this group caused by achromobacter sepsis while he was being given inappropriate treatment with antibiotics, and 4 of the survivors have had, or will need, minor reparatory surgery to their umbilical defects. One child in this group was diagnosed as having mercury intoxication due to mercurochrome applications. He had a 9 cm defect (Fig. 1) and after initial sepsis and respiratory failure requiring ventilation failed to thrive at age 8 weeks (Fig. 2). Mercurochrome 2% had been applied daily to wet areas. At this stage we proceeded with pure alcohol solutions as the only application and he then showed satisfactory weight gain (Fig. 3). One other patient in the series is mentally retarded with microcephaly. We believe this may be a case of undiagnosed mercury intoxication. Patients treated conservatively stayed in hospital for a time varying between 6 and 16 weeks.

Discussion

The object of treatment of these children should be primarily to save life, but an important consideration is to achieve a sound abdominal wall with as short a stay in hospital as possible. In this hospital there has

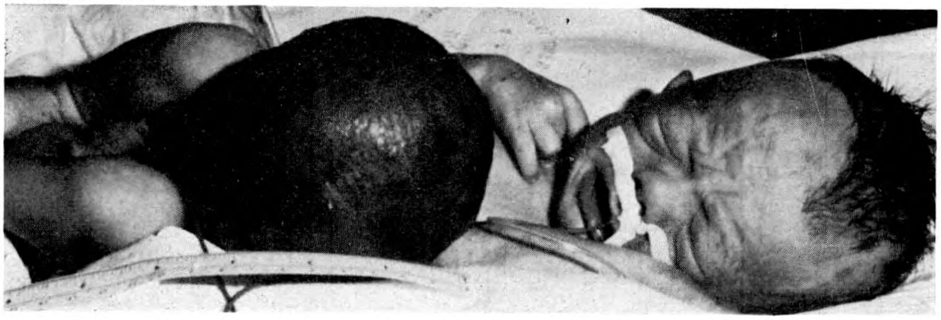

Fig. 1 *Case 1. Mercurochrome treatment aged one day.*

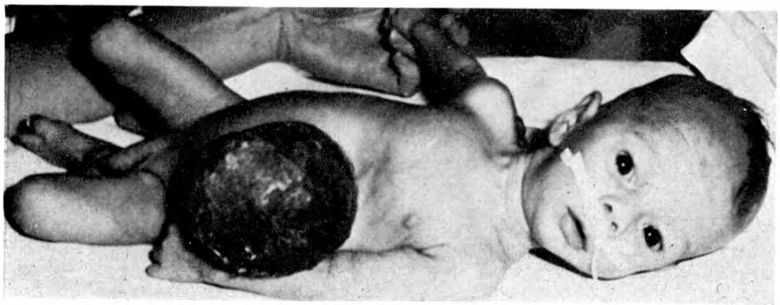

Fig. 2 *Case 1. Mercurochrome treatment aged 8 weeks.*

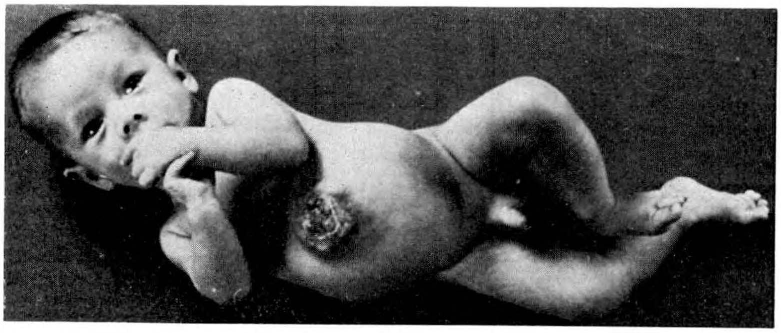

Fig. 3 *Case 1. Mercurochrome treatment aged 11 months.*

been an overall improvement in results: in 1952–62 there were 3 survivors out of 13 patients (Jones, 1963), in 1967–77 there were 12 survivors out of 17 patients. Improvements in the supportive care, particularly better respiratory support and nutritional techniques, seem primarily responsible for the higher rates of survival.

Several reports have confirmed the safety of non-operative treatment (Grob, 1957, 1963; Soave, 1963; Firor, 1971; Ryan, 1973). Even among the writings of surgeons who favour an aggressive surgical approach there are reports which show 28 survivors from 34 patients treated conservatively (Kim, 1976) These figures are mirrored closely by current results.

We are not aware of any substantial series of patients treated by the Shuster method that has better results. In fact Shuster's original series of 11 neonates with intact exomphalos treated by his own method, remains the largest single series and is still the most successful, with 9 patients surviving.

More recent and smaller series have shown mortality rates to be between 33 and 50% (Gilbert *et al.*, 1968; Ryan, 1973). A combination of staged reduction with skin or sialon prosthesis achieved good results in all 4 patients operated on by Mahour *et al.* (1973). Some arguments support operative management and emphasise that other anomalies may be present—such as gut atresia or diaphragmatic hernia (Mahour *et al.*, 1973). In our experience these anomalies can be diagnosed by clinical and radiological examination and, if present, may dictate a purely surgical approach, although their surgical correction may not of course prevent mortality.

The long-term aim of a soundly healed abdominal wall can be achieved in most patients by either technique. Secondary surgery will be necessary in many patients, as shown in this series and confirmed by others (Shuster, 1967; Gilbert *et al.*, 1968), but the extent of operation is usually less in those who have been treated conservatively initially.

Sepsis is now the overriding problem in all methods of treatment. These patients stay a long time in intensive care units, and the use of systemic antibiotics and local antiseptics does not always prevent severe and sometimes life-threatening infections. This complication was responsible for the 3 preventable deaths in our series. Our experience has been that appropriate treatment with antibiotics controls sepsis more effectively in the absence of a foreign body prosthesis.

The risk of mercury poisoning with the use of mercurochrome has been emphasised (Fagan *et al.*, 1977). We believe this can be overcome by using mercurochrome without the impurity of free mercury and by using it only for a short period. We have also experimented with the use of a drying agent—such as alcohol not containing mercurochrome.

Other complications of conservative treatment—such as volvulus (Grob, 1963)—have been seen with the use of sialon prosthesis, but we did not encounter them. Since completing this series we have had one patient in whom the exomphalos sac ruptured while undergoing conservative treatment; this was successfully treated with a sialon prosthesis.

As long periods of stay in hospital are necessary in all forms of treatment, we encourage the parents to participate in the treatment of the child (Fig. 4).

Conclusions

At the Royal Children's Hospital, Melbourne, the survival of infants with intact giant exomphalos has improved significantly since the reported

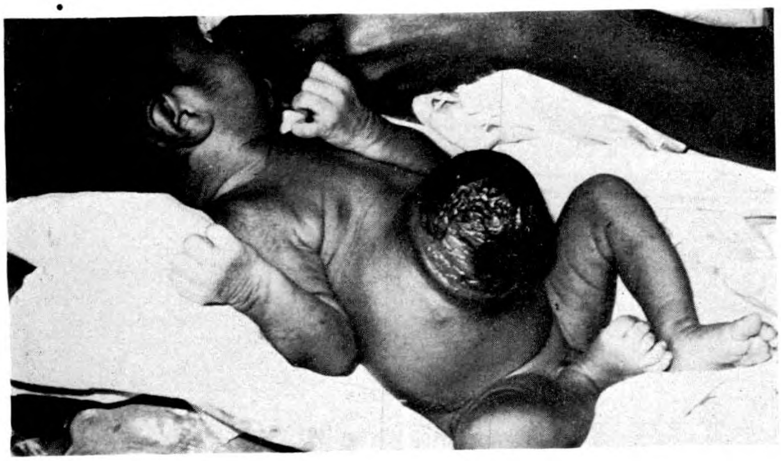

Fig. 4 *Case 2. Mercurochrome treatment aged 2 weeks, breast feeding.*

mortality for the period 1952–62 of 75%, to 12 survivors in 17 patients in the current series. Improved respiratory support, intravenous nutrition, and new antibiotics have all contributed.

The results now reported indicate that if primary operative closure is not possible there is little difference in mortality between nonoperative management and staged operative closure using a sialon prosthesis.

We thank the staff of the Royal Children's Hospital for permission to publish these results.

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Defective Candida killing in childhood malnutrition

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SUMMARY This study shows that malnourished children have impaired candidacidal activity of leucocytes, a finding which runs parallel to the higher rates of isolation of *Candida* sp. from throat secretions. In well nourished subjects the mean candidacidal ability was 44·5%, in the moderately undernourished group it was 17·6%, and in the severely malnourished group it was 13·7%. This impaired candidacidal capacity may be important in the establishment of large numbers of *Candida* sp. which are commonly found in the upper intestine and in the pathogenesis of diarrhoea in children with malnutrition.

Candida species are common in the upper intestinal contents of malnourished children (Mata *et al.*, 1972; Gracey *et al.*, 1974) and may contribute to the production of diarrhoea by their effects on intestinal absorption of sugar (Burke *et al.*, 1977) and water (Thelen *et al.*, 1978). The mechanism by which such large numbers of *Candida* become established in malnourished children is not clear. Previous studies have shown the ability of such children to secrete intestinal immunoglobulins to be unimpaired (Bell *et al.*, 1976), while depression of cell-mediated immunity *in vivo* and *in vitro* has been reported in malnutrition (Geefhuysen *et al.*, 1971; Chandra, 1972; Ferguson *et al.*, 1974). However Kulapongs *et al.* (1974) found lymphocyte responsiveness to phytohaemagglutinin and killing ability of polymorphs to be normal in a group of malnourished children with iron deficiency, while Macdougall *et al.* (1975) found cell-mediated immunity was impaired in such children. Bactericidal function of polymorphs was assessed using *Escherichia coli* as the test organism in the study of Kulapongs *et al.* (1974), but Macdougall *et al.* (1975) and other investigators, showing impaired killing ability of polymorphs (Seth and Chandra, 1972), used staphylococci. It may be that bactericidal function is reduced only in relation to specific organisms.

Lehrer and Cline (1969) showed that leucocytic function was important in resistance to Candida infection. Using their technique, it was shown that the Candida-killing ability of polymorphs is reduced in newborn babies, a group known to be susceptible to mucosal candidal infections (Xanthou *et al.*, 1975). Because of our interest in gastrointestinal candidiasis in malnourished children we investigated the Candida-killing ability of polymorphs in such children.

Materials and methods

Patients. Blood and throat swabs were obtained from 67 children and adults. Patients were classified according to the recommendations of the Wellcome Working Party (*Lancet*, 1970) into a normal group with body weights >80% standard weight for age (SWFA), an underweight group 60–80% SWFA, and a marasmic group <60% SWFA. Samples of 4 ml heparinised blood were obtained by venepuncture from normal adults, well nourished children without known immunological deficiencies attending Princess Margaret Hospital in Perth, Indonesian children admitted to hospital in Jakarta, and from Australian aboriginal children in hospital in Derby, an isolated country town on the coast in the far north of Western Australia.

Candida-killing ability of leucocytes. The method of Lehrer and Cline (1969) was used with the modifications of Xanthou *et al.* (1975) to minimise the volume of blood taken from the children. Killing

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ability was measured by counting the number of Candida stained by methylene blue which distinguishes killed organisms, after incubating comparable numbers of neutrophils and viable Candida in serum with Hanks's solution for 30 minutes at 37°C. All tests were done using patients' sera as well as with normal adult sera. At least 300 cells were counted for each sample and results are expressed as the number killed—that is, blue-stained Candida/100 phagocytosed organisms. Differences in percentage of Candida killed in groups classified according to nutritional status were assessed using the Kolmogorov-Smirnov test.

Throat swabs. Specimens were collected into Stuart's transport medium and refrigerated at 4°C if not processed immediately. Those from Derby and Jakarta were flown to Perth on ice and processed within 24 hours of collection. Throat swabs were cultured in Sabouraud's dextrose agar and incubated for 48 hours at 25°C.

Results

Candida-killing ability was not related to age, race, or diagnosis on admission to hospital. Consequently, results were considered only in relation to the patient's nutritional state.

In the well nourished group the mean candidacidal ability was 44·5% (SEM 8·8), for those with weights 60–80% SWFA the mean was 17·6% (SEM 4·4), and for children with weights <60% of SWFA the mean was 13·7% (SEM 3·4). Results are shown in the Figure. Comparison of each malnourished group with the well nourished subjects showed the difference to be highly significant (P<0·001). However, there was no significant difference in candidacidal ability between the two groups of malnourished children. Addition of normal sera in place of the patients' own sera did not alter the Candida-killing ability of their leucocytes.

We previously showed (Gracey *et al.*, 1973) that oropharyngeal flora probably reflect environmental contamination, so that it is invalid to compare isolation rates of organisms from such different areas as Perth, Derby, and Jakarta. As there were no malnourished children from Perth, results of throat swabs taken in Perth were not included in the analysis. Children from Derby and Jakarta were grouped according to nutritional status and separate comparisons made for each area. In Jakarta, 92% of malnourished children had *Candida* in their throat swabs compared with 66% of normal children; in Derby *Candida* was grown from throat swabs of 80% of malnourished children but from only 14% of normal children.

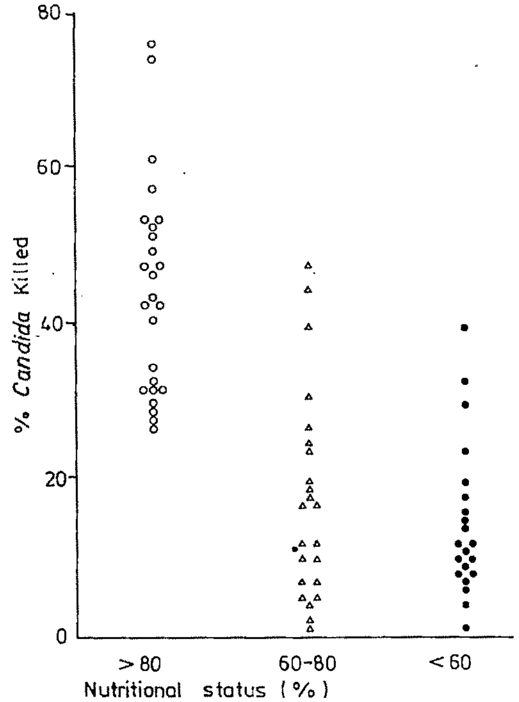

Figure *Candida-killing capacity (expressed as percentage of Candida killed) according to nutritional status expressed as a percentage of standard weight for age compared with the 50th centile of the Harvard standards (Lancet, 1970).*

Discussion

We show that malnourished children have reduced candidacidal activity of their leucocytes. This finding runs parallel to the higher isolation rate of *Candida* sp. from throat swabs of malnourished children. The defective Candida-killing ability of these leucocytes was not corrected by adding normal serum. Lehrer and Cline (1969) found that serum factors did not affect the candidacidal property of leucocytes and the addition of normal serum did not correct defective Candida-killing by leucocytes in the newborn (Xanthou *et al.*, 1975). It would seem that malnourished children also have impaired leucocyte function in relation to *Candida* killing. We found that the Candida-killing ability of leucocytes was reduced in patients with a high isolation rate of *Candida* sp. from their throat swabs. Organisms isolated from the upper small bowel are similar to the flora of the oral cavity (Dickman *et al.*, 1976) and our previous investigations suggest that *Candida* sp.

are likely to be found in the upper intestinal contents of these children (Gracey *et al.*, 1974). The relationship between gastrointestinal infection with *Candida* sp. and impaired *Candida*-killing ability of leucocytes is not clear. Although several investigators have established the importance of intestinal antibodies in controlling bacterial contamination of the upper intestinal contents (Walker and Isselbacher, 1977), their role in relation to intestinal candidiasis is not known. However, malnutrition does not impair secretion of immunoglobulins into the intestinal lumen as intestinal immunoglobulin levels have been shown to be raised in malnourished children with infections (Bell *et al.*, 1976). The importance of leucocytic function in maintaining the relative sterility of upper intestinal contents has not been widely investigated. However Takeuchi *et al.* (1965) and Kenworthy (1970) showed that phagocytosis was important during the establishment of experimental infections with *Shigella* and *E. coli.* It may be that neutrophils are also important in controlling candidal infections in the small intestine.

Our findings show that polymorphs from malnourished children have an impaired ability to kill Candida and extend the observation that the ability to kill *Staphylococcus pyogenes* is reduced in malnutrition (Seth and Chandra, 1972). This mechanism may contribute to the significantly increased incidence of candidal infections in malnourished children.

We thank everyone in Australia and Indonesia who took part in this study, and the doctors and nurses who helped to collect and transport the specimens.

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Bronchial asthma in Nigerian children

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SUMMARY Clinical and laboratory studies on bronchial asthma in 200 Nigerian children who were seen during a 2½-year period in Ibadan are described. Contrary to reports that the condition is rare in African children, after pulmonary tuberculosis, asthma is the next most common chronic chest disease in Ibadan. While many features of the disease are similar to those seen elsewhere, skin tests indicate that ascaris is the most common antigen associated with asthma, followed by *Dermatophagoides pteronyssinus*.

Bronchial asthma, a common childhood chronic respiratory problem in the West (Godfrey, 1974), is reported to be rare among African children (Wesley *et al.*, 1969; Godfrey, 1975; Warrell *et al.*, 1975).

While studies by Mitchell (1970), Sofowora (1970), Anim and Edoo (1972), and Buchanan and Jones (1972) showed that the condition is common in African adults, Wesley *et al.* (1969) reported that bronchial asthma is extremely rare among Bantu children in South Africa. In Nigeria, Warrell *et al.* (1975) reported that asthma is rarely seen in children living in the savanna region of the country. Our experience at this hospital in Ibadan during the last few years indicates that the condition is far more common in children here than these reports suggest. This paper gives the results of studies on 200 asthmatic children seen at this hospital during a 2½-year period (June 1974 to December 1976).

Materials and methods

The patients in this study were referred to the chest clinic mainly from the general outpatient department of the hospital but some came from private clinics and hospitals in Ibadan and nearby. Diagnosis of asthma was based on a history of at least three attacks of breathlessness and wheezing (Blair, 1969), often associated with cough, and usually supported at the time of initial examination or during subsequent follow-up, by the auscultatory finding of widespread respiratory rhonchi. In some patients who presented in acute attacks, the diagnosis was further supported by the demonstration of at least 20% increase in the peak flow (measured with a Wright's peak flow meter) after the administration of a bronchodilator.

Laboratory investigations carried out on the patients included packed cell volume, white blood count—total and differential—stool microscopical examination, chest *x*-rays, and in a few children, the radiology of the paranasal sinuses. Skin sensitivity tests were done by the prick method, using a selected range of commercially prepared allergen extracts (Bencard). The weal diameter of the reaction recorded was the difference in mm between it and the control. Weals of at least 2 mm in diameter were regarded as positive (Pearson, 1973).

The children were classified into three groups according to the severity of the disease. This grading system was modified from one described by Dawson *et al.* (1969). The *severe* group consisted of patients with more than 10 acute attacks a year with or without complete clinical recovery between attacks. The *moderate* group had 5 to 10 attacks a year and usually showed complete or partial freedom from wheezing between attacks, while the *mild* group had 1 to 5 attacks a year with complete clinical recovery between attacks.

Results

Age at presentation and sex incidence. The children were aged between 10 months and 13 years; 97 (49%) of them were less than 5 years. The boy/girl ratio was 1·6:1.

Age of onset. As shown in the Figure, 125 (63%) children had their first attacks before age 3 years.

Referral diagnoses. Diagnosis of asthma or asthmatic bronchitis was made before referral in 136 (68%)

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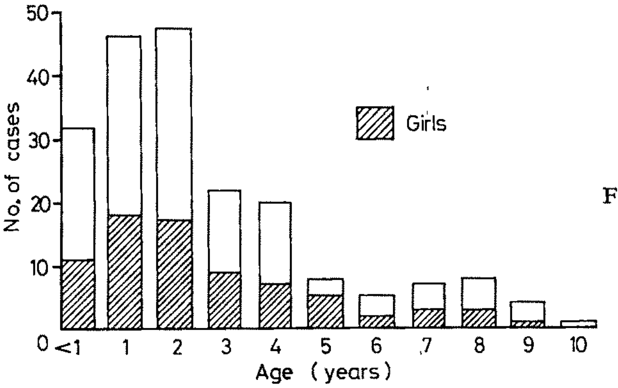

Figure *Age of onset in 200 children with asthma.*

cases, while 18 (9%) were referred as cases of pulmonary tuberculosis, 15 as cases of bronchopneumonia, and 5 (3%) were thought to be cases of acute bronchitis or bronchiolitis. Other referral diagnoses included chronic bronchitis, chronic chest infection, and lobar pneumonia. In 15 cases, no diagnosis had been entertained at the time of referral.

Early feeding. 166 (98%) of 170 children whose early feeding histories were reliably ascertained were breast fed from birth. This is similar to the rate of 99% in 385 Ibadan women from all social classes who breast fed (Omololu, 1972). 145 (85%) of the same 170 children were fed on artificial milk, generally in addition to the breast milk; in 55% of them this was from the first week of birth. This proportion of those fed on artificial milk contrasts with 78% (range 45% in illiterate women to 99% in 'élites') of the women in Omololu's series who fed their children partially or wholly on artificial milk.

Family and social histories. Table 1 shows that there were 127 (63·5%) patients who came from the upper socioeconomic classes (classes I, II, and III). This compares with an estimated 20% of these three classes attending hospital for other respiratory complaints. There was a positive family history of allergy in 79 (40%) of the 200 patients. 73 of these were siblings or parents suffering from asthma, but 5 parents had allergic rhinitis, and one sibling suffered from eczema. 78 (39%) of the 200 children were attending school, and of these, 14 were often absent from school because of asthmatic attacks. 74 (38·9%) of 190 families had domestic animals or pets—such as chickens, dogs, cats, or goats.

Precipitating and associated factors. There was a positive history of precipitating factors in 155 (78%) of cases (Table 2), leaving 45 cases where there was none.

Presenting symptoms. The predominant symptom was breathlessness during attacks noted in all 200 children. Cough and wheezing were the next most common, both occurring in 96% of children. Other common and frequent symptoms included sweating (most profuse on the forehead during acute attacks), anorexia and loss of weight, which occurred while the attack lasted and abated soon after it ceased. Symptoms of chest pains and headaches were given by patients older than 5 years. Sputum, mixed with

Table 1 *Professional/social classes of fathers of 200 asthmatic children*

Social class	*Profession*	*No. of cases*	*% of total*
I	Academic professionals, senior administrators, owners of large business firms, military officers	40	20
II	Nonacademic professionals	25	12·5
III	Clerical workers, skilled workers, and artisans	62	31
IV	Semiskilled workers	40	20
V	Unskilled workers and petty traders	32	16
VII	Students	1	0·5

Table 2 *Major precipitating and associated factors in the history of 200 cases of bronchial asthma*

Factor	*No. of cases*	*% of total*
Night-time	87	43·5
Exercise	60	30
Rainy season	47	23·5
Cold season	18	9
Specific foods	16	8
Fever	16	8
Cold bath	15	7·5
Cold water drink	10	5
Excitement	9	4·5
Fan	9	4·5
Dry season	7	3·5
Dust	5	2·5

streaks of blood (often slight and infrequent), was present in 8 (4%) patients.

Physical signs

Physical growth

Weight and height were recorded in 169 patients at the first visit to the clinic, and weight alone was recorded in 28 others. The figures were plotted on centile charts for British children (Tanner *et al.*, 1966). According to Janes (1970), the weights and heights of élite or privileged Nigerian children of both sexes compare favourably with those of British children, hence the use of British centile charts. 63 (32%) of the 197 children had weights <10th centile, while 151 (77%) were <50th centile. The corresponding figures for heights were 40 (24%) of 169 <10th centile and 109 (65%) <50th centile.

Respiratory signs

No abnormal auscultatory signs were present in 102 (51%) of the 200 cases at the initial visit. There was audible wheeze in 30 of the remaining 98 patients, and the other children had abnormal signs only on auscultation. These abnormal auscultatory signs consisted of inspiratory and expiratory rhonchi in 59 children, expiratory rhonchi alone in 23, inspiratory rhonchi alone in 8, and combined rhonchi and crepitations in the remaining 8 patients. There was a barrel-shape chest deformity in 19 (10%) of the 200 patients.

Other signs

10 children (5%) had flexural eczema which had been present from infancy in 2 of them and was quiescent in 7 others; vernal conjunctivitis was present in 19 (9·5%) patients.

Severity of asthma

58 (29%) of the 200 patients were classified as having severe asthma, while 30 (15%) had a moderate type, and in 112 (56%) of them it was mild.

Investigations

Skin sensitivity tests. Skin tests were performed on 139 children using between 10 and 30 allergen extracts. The results were negative in 46 (33%) of the children. Table 3 shows the 10 most common allergens to which the remaining 93 patients were sensitive. Ascaris antigen topped the list of positives, followed by *Dermatophagoides pteronyssinus* and house dust.

Table 3 *Skin reactions to individual allergens**

Allergen	*No. tested*	*% positive*
Ascaris	77	34
D. pteronyssinus	139	22
House dust	115	18
Flower and shrub pollens	77	18
Cat fur	115	16
Grass pollen	139	14
Feathers	115	12
Fish	77	11
Meat	77	11
Cockroach	77	9

*Other allergens tested were cows' milk, whole egg, tree pollen, mixed yeast, *Aspergillus fumigatus*, dog hair, goat hair, fruits, plantain, horse hair, moulds (A13, M5, M10, M11), cereals, cotton flock, mosquito, sheep wool, human hair, and chocolate.

Table 4 *Chext x-ray findings at presentation in 190 asthmatic children*

Finding	*No. of cases*	*% of cases*
Normal	59	31
Increased linear lung markings alone	40	21
Increased linear lung markings and increased hilar shadows	21	11
Inflammatory changes/bronchopneumonia	39	21
Peribronchial thickening	24	13
Hyperinflation	4	2
Lobar consolidation	2	1
Calcification and inflammatory changes	1	0·5

Chest x-rays. The findings in 190 cases are shown in Table 4. 99 (52%) of the 190 had normal films or a slight linear increase in lung markings. Only 4 (2%) showed evidence of hyperinflation (most of the films were not taken during acute attacks). It is noteworthy that 11% of the patients had increased lung markings and increased hilar shadows mimicking hilar lymphadenopathy.

Paranasal sinus x-rays. These were done in 32 patients, 22 (69%) of whom had normal sinuses while 8 (25%) showed thickening of the mucosa; clouding of the sinuses was evident in only 2 children.

Blood eosinophilia and stool parasites. The mean eosinophil count in 168 children was 1166/mm^3 (1·1 × 10^9/l) (range 0–5562/mm^3; 0–5·5 × 10^9/l), compared with a mean count of 449/mm^3 (0·4 × 10^9/l) (range 0–1425; 0–1·4 × 10^9/l) in a group of 50 control children. In all, 67 (40%) of the 168 had eosinophil counts >1000/mm^3 (1·0 × 10^9/l). In relation to the total white blood count, the mean percentage was 13% (range 0–42%), compared with a mean of 5% (0–23%) for the controls. 87 (52%) of the 168 had percentages >11%.

Stool specimens from the children were examined at the same time that the eosinophil counts were done. Helminths, mainly the ova of ascaris and trichuris, were present in the stools of 120 of these patients. The eosinophil count (mean 1362/mm^3;

$1 \cdot 3 \times 10^9/l$) in asthmatic children with stool parasites was higher than the counts in those without parasites (mean 787/mm^3; $0 \cdot 7 \times 10^9/l$). However, in a group of 35 controls with stool parasites, the eosinophil count (mean, 510/mm^3; $0 \cdot 5 \times 10^9/l$) was lower still, suggesting that both the atopic state and helminthiasis contributed to the high eosinophil count in the patients with asthma.

Tuberculin skin test. These were carried out in 183 of the children. 102 (57 %) of these had negative tuberculin reactions while 75 (41 %) and 6 (3 %) had grades 1 and 2 respectively. In none of the children was there any other evidence of tuberculosis.

Haemoglobin electrophoresis. 179 children had genotype determinations. Of these, 140 had the normal A genotype while 39 (22 %) had abnormal genotypes (AS, 31; AC, 6; SC, 1; SS, 1). This proportion of abnormal Hb electrophoretic pattern is similar to that in the general population.

Discussion

Most of the features of asthma in the present series are similar to those described in children elsewhere. The male preponderance is in keeping with the findings of Dawson *et al.* (1969), and Davis (1976). 63 % of our patients had their first attacks of wheezing before age 3 years, similar to the findings of Wesley *et al.* (1969), but higher than the 44 % reported by Dawson *et al.* (1969) and the 32 % reported by Williams and McNicol (1969). Other similarities with the situation in the UK or Australia are found in the proportion of patients with a family history of allergy and in the common precipitating factors. Contrasting with these similarities, there are certain dissimilarities, notably the finding that the ascaris antigen was the most common allergen to which the skins of the children were sensitive. This sensitivity bore no consistent relationship with the presence of ascaris ova in the stool. Although the full significance of this finding is not clear, none of the 35 controls who has so far undergone skin tests with the ascaris antigen has had a positive reaction. Another dissimilarity is the proportion of children showing negative skin reactions to a battery of between 10 and 30 antigens. In the present series, 33 % of the children tested did not react to any antigen, including *D. pteronyssinus* and grass pollen. This is in contrast to the 20 % for asthmatic children in Melbourne (Williams and McNicol, 1969) and the 7 % quoted by Godfrey (1974) in the UK.

The incidence of asthma in European children has been estimated as 0·4 % in Helsinki (Eriksson-Lihr, 1955), 4·8 % in Aberdeen (Dawson *et al.*, 1969), and 9·9 % in Birmingham (Morrison Smith *et al.*, 1971). In Africa, a school survey in Nigeria showed a rate of 2·4 % (Sofowora and Clarke, 1969), and Carswell *et al.* (1977) reported a rate of 7·8 % in a group of Tanzanian children. These estimates, and those of the present series, suggest that bronchial asthma is as common a condition in Ibadan children as it is in European or Australian children. Yet elsewhere in Africa the condition is reported to be rare. In Kenya, the youngest patient reported by Wasunna (1968) in a series of 210 cases was 12. Mitchell (1970) also from Kenya reported that no child under 12 was seen from over 1200 asthmatic patients who attended the Kenyatta National Hospital, Nairobi, and Rees *et al.* (1974), reporting on 124 asthmatic cases from the same hospital, recorded only 18 patients under 21 years. In South Africa, Wesley *et al.* (1969), comparing the incidence of asthma in Durban children of three racial groups, concluded that bronchial asthma was extremely rare among Bantus. Warrell *et al.* (1975) reported that only one child was admitted with severe asthma during a period of 4 years in Zaria, Northern Nigeria, an area where the paediatric outpatient attenders number approximately 96 000 children each year. It thus appears that while the prevalence of asthma among adults is similar in many parts of Africa, there are wide variations in its prevalence in childhood. This variation may be attributed to the fact that the children in different areas of Africa are not exposed to adverse environmental precipitating factors—such as artificial feeding, atmospheric pollution, and other allergens—in the same way and at the same ages. Another possible explanation may be the difficulty in differentiating bronchial asthma from other forms of chronic respiratory disorders affecting children in Africa.

The fact that the diagnosis of bronchial asthma in environments such as ours depends mainly on its clinical features (provocation tests cannot easily be carried out), makes it inevitable that mistakes in diagnosis are common. Bronchial asthma can easily be confused with pulmonary tuberculosis, a common condition in African children, with the cardinal symptoms of cough, fever, anorexia, loss of weight, and night sweats, which also occur with bronchial asthma. (Even haemoptysis was present in 4 % of the cases in this series of asthma.) 9 % in the present series of asthmatic children were diagnosed as pulmonary tuberculosis before referral, and 2 of these were treated with antituberculous drugs for a prolonged period before the correct diagnosis was made. To avoid misdiagnosis, as great an emphasis should be placed on the history of recurrent attacks of breathlessness as on wheezing, for it is much easier to obtain a history of breathlessness than of wheezing in Africa where there are often no vernacular equivalents of the word, and where to elicit such symptoms the examiner must be able to mimic the wheezing sound.

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Dr R. H. Dobbs, formerly Professor of Paediatrics in Zaria, Northern Nigeria, was invited to comment on this article.

This paper illustrates the difficulties in assessing the many environmental factors—social, ethnic, and climatic—that interact to bring out clinical manifestations in atopic children.

Climate is undoubtedly crucial and it is made clear, both in the text and in Table 2 of this paper, that in Ibadan, less than 100 miles from the south coast, the rainy season is an important precipitating factor of asthmatic attacks, whereas in Zaria, 100 miles from the northern frontier, where the dry season often extends throughout 9 or 10 months of the year, childhood asthma scarcely exists, and those few cases that are encountered there, are in the neighbouring densely urban town of Kaduna, and confined to the few rainy months.

Social class appears also to have much bearing on the incidence of childhood asthma and its delayed appearance until early adolescence. As recorded, in Ibadan 64% of patients were drawn from the relatively wealthy classes I to III, in contrast to only 20% attending with other respiratory illnesses. The almost universal reliance on breast feeding, and the late onset of cows' milk supplements in the poor may be an important factor in this delay, although the data are not sufficiently clear to draw conclusions.

It may be added that it is now thought that the protective factors in breast milk are more important than any immunologically deleterious action of cows' milk. But perhaps of even greater importance is the enormously high infant mortality rate, which may well lead to the elimination of a large proportion of the undernourished, immunologically deficient, and atopic infant population of the poorer classes, with the rich paying for their Darwinian survival with the development of childhood allergy.

The high frequency of positive skin tests to ascaris is of great interest, being in confirmity with previous studies. This does not necessarily mean that ascaris antigen is responsible for triggering the asthmatic state. Indeed it has been suggested that, on the contrary, because of high levels of IgE antibody to ascaris, most cell-binding sites may be blocked for antibody to other antigens, and thereby protect against asthma. This concept might seem to be countered by the author's statement that ' None of the 35 controls . . . has shown positive reactions (to ascaris)', an observation that is hard to understand in view of the worm infestation of African children in general.

A final point relating to the incidence of asthma in developing countries, although not discussed in this paper, is worth consideration—the rarity of asthma in young children of some localities and social classes is in contrast with its development as adolescence approaches. This is illustrated by the need to set up asthma clinics in Northern Nigeria; these are found to deal almost entirely with adult asthmatics. It seems that environmental factors can, with the passage of time, induce atopic disorders.

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Carbamazepine dose-frequency requirement in children

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SUMMARY The dose-frequency requirement for carbamazepine (CBZ) in children was investigated using serial saliva samples to determine the daily fluctuation in drug levels. Mixed saliva was collected from 6 children (aged between 6 and 13 years) in a steady state, on each of two different dose-frequency regimens of once to 3 times daily, with a constant total daily dose. Increasing the dose-frequency resulted in smaller fluctuations in saliva concentration and a shorter time with levels outside the therapeutic range. Toxic features and convulsions appeared to be related to peak and trough concentrations. There was no apparent relationship between the total dose and the mean saliva concentration. The saliva CBZ half-lives in 2 children were 7·3 and 12·7 hours, and the apparent volumes of distribution (saliva) were 1·6 and 1·5 l/kg respectively. Saliva CBZ concentrations are an efficient and convenient means of tailoring individual dosage, and can be used to provide the pharmacokinetic data that rational prescribing demands.

Plasma level monitoring of anticonvulsant drugs in the management of convulsive disorders is being used increasingly (Kutt and McDowell, 1968; Kutt and Penry, 1974). The practice is now routine in most centres for phenobarbitone and phenytoin, for which established therapeutic ranges exist. For carbamazepine (CBZ), a therapeutic plasma concentration range in adults has been suggested from studies relating plasma levels with clinical effects (Morselli and Frigerio, 1975; Troupin *et al.*, 1975).

Saliva drug levels as a substitute for plasma levels have been shown to be useful for some anticonvulsant drugs in adults (Schmidt and Kupferberg, 1975; Troupin and Friel, 1975; Reynolds *et al.*, 1976), and for CBZ in children (Bartels *et al.*, 1977; Rylance *et al.*, 1977). The saliva levels of phenytoin, phenobarbitone (after correcting for saliva pH), and CBZ are similar to the concentrations of the free or unbound drug in plasma water (Schmidt and Kupferberg, 1975; Troupin and Friel, 1975; McAuliffe *et al.*, 1977), and may therefore be of greater therapeutic significance than the plasma concentration.

Some drugs are eliminated more rapidly by children than by adults (Svensmark and Buchthal, 1964; Borofsky *et al.*, 1972; Chang *et al.*, 1972), and the half-life of CBZ in 3 children receiving long-term treatment was reportedly shorter, 7·3–18·9 hours (Rane *et al.*, 1976; Rylance *et al.*, 1977), than in adults, 16·4–36·5 hours (Eichelbaum *et al.*, 1975; Faigle *et al.*, 1976). One consequence of this is that similar dosage produces lower steady-state drug levels in children than in adults (Morselli *et al.*, 1975; Monaco *et al.*, 1976). In addition, faster drug elimination would be expected to produce greater fluctuations in drug levels in children on a similar dose-frequency regimen as adults. Because of this and other pharmacokinetic factors, the dose-frequency regimens recommended for use in adults may be inappropriate for use in children.

In this study, the influence of dose-frequency on saliva CBZ levels was determined in a group of children.

Methods

Six children aged between 6 and 13 years attending the outpatient clinic of Ninewells Hospital, Dundee, were studied; approval was granted by the local hospital ethical committee. All children had received treatment with CBZ for at least 12 weeks before the study began, 3 receiving CBZ alone, and 3 receiving either phenytoin or ethosuximide in addition to CBZ.

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Mixed saliva was collected after stimulation with citric acid and flavouring (Bacon *et al.*, 1978) at approximately hourly intervals from 0900 to 2300 hours and from 0600 to 0900 hours the next day, the children spending the night in hospital. This procedure was carried out twice for each child. The total daily dose remained constant each time, but the dose-frequency was changed so that 2 children received CBZ once daily on the first occasion and twice daily on the second, and the other 4 received the drug two- and three-times daily (Table 1). The approximate times of CBZ administration were: once daily 0900 hours; twice daily 0900 and 2100 hours; thrice daily 0900, 1600, and 2300 hours. The children were maintained on each dose regimen for at least 6 days before saliva sampling, to enable a steady state to be reached.

Proprietary CBZ tablets were used except in Cases 4, 5, and 6 on thrice-daily regimens, when part of each dose was given as powdered proprietary tablet. To avoid contamination of the initial samples by CBZ retained in the mouth, the children swallowed water to rinse their mouths and brushed their teeth.

Saliva samples were stored at −20°C until assayed for CBZ by a modification of the method for serum described by Least *et al.* (1975). 2 ml saliva were added to a 10 ml glass-stoppered tube containing 5 ml chloroform, 1 ml 0·5 M sodium hydroxide, and 0·1 ml codeine in chloroform, 268 μmol/l (internal standard). The mixture was shaken vigorously for 10 min and the aqueous layer was removed and discarded. The organic layer was transferred to a tapered glass-stoppered tube and evaporated to dryness under nitrogen at 45°C. The sides of the tube were washed with 0·5 ml chloroform and evaporated as before. The residue was dissolved in 10 μl dry pyridine and 20 μl N,O-bis-(trimethylsilyl)-acetamide, incubated for 30 min at room temperature, and 1 μl aliquots injected into the GLC column. A Pye 104 gas chromatograph with dual flame ionisation detectors was used. The glass columns were 2 m × 4 mm in diameter, packed with 3% OV17 on Gas Chrom Q 100/120. Operating conditions were: injection port 300°C, oven 240°C, detector 300°C, nitrogen 50 ml/min, hydrogen 50 ml/min, air 250 ml/min. The sensitivity of the assay enabled the determination of CBZ down to 2 μmol/l. The mean coefficient of variation of the method over the concentration range 2–70 μmol/l was 3·5%.

The area under the CBZ concentration-time curve (AUC) was calculated for one dose interval (τ) for each child on each regimen using the trapezoidal rule. The mean steady-state saliva CBZ concentration ($\bar{C}_{ss}S$) was then calculated from the relationship, $\bar{C}_{ss}S = AUC/\tau$.

The daily fluctuation in saliva drug levels was expressed as a percentage thus:

$$\text{Fluctuation} = \frac{(\text{Highest} - \text{lowest concentration})}{\bar{C}_{ss}S} \times 100\%$$

The first-order elimination rate constant (k) in Cases 1 and 2 receiving the drug once daily was obtained from the regression line fitted to the logarithm of the saliva concentration versus time curve by the method of least squares.

Clearance (C), the apparent volume of distribution (Vd_{ss}), and the saliva half-life ($t\frac{1}{2}$) were calculated from the saliva data using the equation:

$$\bar{C}_{ss}S = \frac{F \,.\, D}{k \,.\, Vd_{ss} \,.\, \tau}$$

where D is the dose given at each time interval (τ), $C = k \,.\, Vd_{ss}$, $t\frac{1}{2} = 0{\cdot}693/k$, and F = fraction of dose absorbed, assumed to be unity.

Results

The 24-hour saliva CBZ concentration profiles of the 6 children on each regimen are shown in the Figure. The therapeutic range in saliva (5·5–15 μmol/l) was derived from the reported saliva/plasma

Table 1 *Mean steady-state saliva carbamazepine concentrations and the daily fluctuation in concentration in children on different dose-frequency regimens*

Case	*Sex*	*Age (years)*	*Dosage (mg/kg)*	*Other drugs*	*Once daily*		*Twice daily*		*Thrice daily*	
					Concentration (μmol/l)*	*Fluctuation (%)*	*Concentration* (μmol/l)*	*Fluctuation (%)*	*Concentration* (μmol/l)*	*Fluctuation (%)*
1	M	6	27	—	8·7	160	8·0	74		
2	M	13	17	Phenytoin	8·9	186	8·8	74		
3	F	13	11	—			13·1	60	13·6	38
4	F	10	37	Phenytoin			12·4	92	10·6	74
5	M	10	21	—			12·6	113	16·3	66
6	M	8	15	Ethosuximide			5·6	212	5·8	60

*Steady-state saliva carbamazepine concentration.
Conversion: SI to traditional units—carbamazepine: 1 μmol/l ≈ 23·6 μg/100 ml.

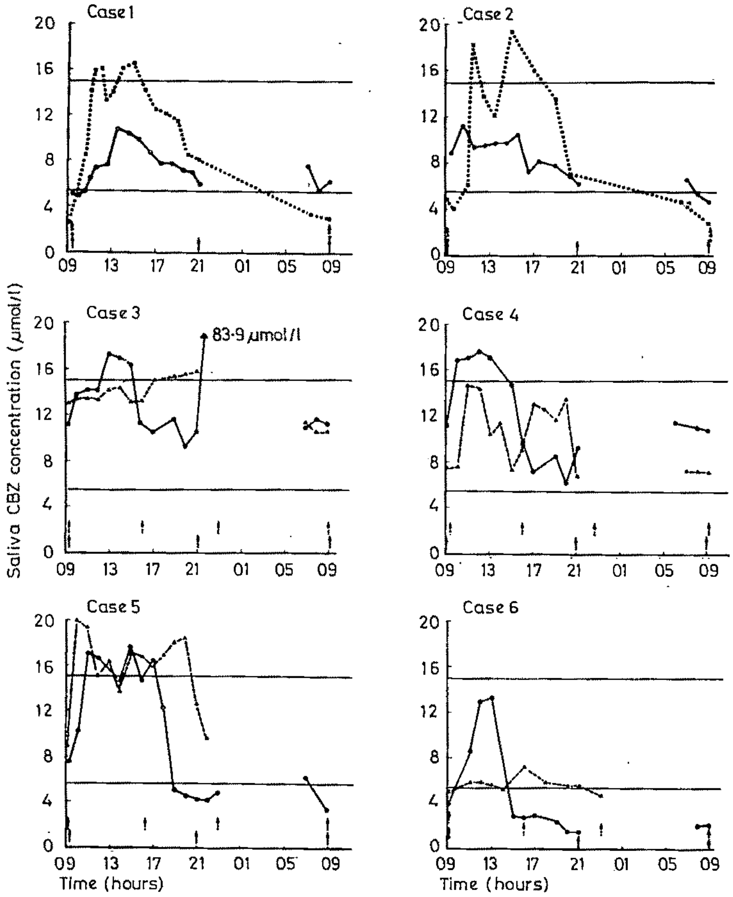

Figure *Saliva carbamazepine (CBZ) concentrations in Cases 1 and 2 on once- (•••) and twice- (●——●) daily dosage, and in Cases 3–6 on twice- (●——●) and thrice (▲------▲) daily dosage. Arrows indicate dose administration times for CBZ given once (↕), twice (↑) and thrice (↑) daily. Horizontal broken lines indicate upper and lower limits of the therapeutic saliva CBZ concentration range.*
Conversion: SI to traditional units—carbamazepine: 1 µmol/l ≈ 23·6 µg/100 ml.

concentration ratio in children (Rylance *et al.*, 1977), and the recommended plasma concentration range in adults (Morselli and Frigerio, 1975; Troupin *et al.*, 1975).

The saliva levels peaked at between 1 and 6 hours, and in Cases 1, 2, 4, and 5, two peaks were observed. There was no contamination except in Case 3 on a twice-daily dosage regimen (Figure). The greatest fluctuation was found in Case 2 receiving CBZ once daily, and the smallest fluctuation in Case 3 on three doses a day (Figure). In all children, increasing the frequency of drug administration resulted in smaller fluctuations in saliva concentration. Frequent drug administration also resulted in a shorter time being spent with saliva levels outside the therapeutic range.

Both children on a once-daily regimen had saliva concentration fluctuations >160% of the mean steady state (Table 1). Increasing the frequency of drug administration to twice daily reduced the fluctuation to <75%. In the 4 other children, the fluctuation fell from 60–213% on twice-daily dosage to 38–75% on thrice-daily dosage.

The mean steady-state saliva concentrations resulting from the two dose regimens in each child, were similar in 4 children and in only 2 (Cases 4 and 5), was the difference >1 µmol/l (Table 1). There was no apparent correlation between the mean steady-state concentration and the total daily dose in any child.

Assuming complete bioavailability, the mean (±SD) saliva clearance of CBZ in the children on twice-daily dosage was 0·398 ± 0·167 l/kg per hour. The saliva CBZ half-lives in Cases 1 and 2 receiving the drug once daily were 7·3 and 12·7 hours, and the apparent volumes of distribution (saliva) for CBZ in these children were 5·78 and 6·12 l/kg respectively.

Toxic features were observed in 2 of the 6 children. Case 1 was ataxic about midday and was often sleepy by midafternoon when receiving CBZ once daily, and Case 3 became dizzy in the early afternoon on twice-daily doses.

None of the children had convulsions during the study period and 3 children had been convulsion-free for the previous 9 months. Two patients had each had one convulsion during the preceding month on their usual dose-frequency regimen, Case 5 at 0800 hours on twice-daily CBZ, and Case 6 at 2300 hours also on two doses a day. Case 4 had had convulsions at approximately monthly intervals during the previous 9 months at varying times of the day, on twice-daily administration.

Discussion

Minimum plasma concentrations and therapeutic ranges for CBZ have been suggested for adults, and the therapeutic concentration range in saliva adopted in this study was derived from these (Morselli and Frigerio, 1975; Troupin *et al.*, 1975), and from the saliva/plasma CBZ ratio in children (Rylance *et al.*, 1977). The mean steady-state saliva concentrations were within this range for all but one child (Case 5), and as expected, the frequency of drug administration did not influence concentration. The higher concentration in Case 5 receiving CBZ three-times daily was possibly a result of the greater bioavailability of the powdered drug used for him, although this was not observed in Cases 4 and 6 who also had part of their thrice-daily doses given in the powdered form.

Although the mean saliva CBZ concentrations indicated that the children were well controlled, there was considerable fluctuation about the mean. The concentrations rose steadily after drug administration reaching peak levels within 1–6 hours in all children, except for Case 3 on twice-daily dosage, in whom the concentration rose immediately after drug administration due to contamination by unabsorbed drug. Contamination was not observed at other times, nor was it observed in the other children. In 4 children the initial peak was followed by a short decline in concentration before peaking again.

The saliva clearance of CBZ was greater than that reported in adults (Westenberg *et al.*, 1978), and together with the two saliva CBZ half-lives which were similar to the plasma half-lives reported for children by Rane *et al.* (1976), indicate that children metabolise CBZ more rapidly than adults do.

A shorter CBZ half-life in children would be expected to produce a greater fluctuation in drug level than in adults, and indeed large variations in saliva concentration were observed in the children receiving the drug once or twice daily. Administration of CBZ thrice daily reduced the fluctuation in saliva drug levels, but large differences between peak and trough levels were still seen in 2 children (Cases 4 and 5). Although the CBZ concentration at the site of action will probably vary to a lesser extent than in plasma or saliva, large fluctuations in saliva will obviously reflect an increased risk of toxicity and/or convulsions. Two of the children in this study (Cases 1 and 3) showed toxic effects when saliva drug levels were at their peak and above the therapeutic range, and convulsions had occurred in two children (Cases 5 and 6) in the preceding month when receiving CBZ twice daily. The seizures occurred just before drug administration when the levels were presumed to be at their lowest.

Johannessen *et al.* (1976) found no direct relationship in adults between the frequency of drug administration and the daily fluctuation in serum levels. However, sampling was probably not frequent enough to detect change in fluctuations arising from the different dose-frequency regimens.

The data from our study suggest that children require more frequent doses of CBZ than do adults. Certainly, once-daily administration results in too great a fluctuation in concentration. Frequent administration may lead to reduced patient compliance, and can prove difficult if the child needs to take the drug during school hours. As many convulsions occur at night (Gibberd and Bateson, 1974), and this is the longest dose interval, it may be possible to improve control by giving a larger dose in the evening.

Single saliva CBZ determinations in children give a poor estimate of the mean steady-state concentration. This is demonstrated when the mean steady-state concentrations obtained for 5 of the children in this study are compared with single outpatient determinations carried out in the same children at random times while on the same dose-frequency regimens (Table 2). The outpatient values differ markedly from the mean steady-state levels.

Serial saliva samples are easily obtained from children of at least 4 years of age, and also from younger children if saliva flow is stimulated and a mucus extractor used (Bacon *et al.*, 1978), but because of possible contamination, care must be

Table 2 *Mean steady-state saliva carbamazepine concentrations and single outpatient levels on the same regimen*

Case	*Dose-frequency each day*	*Concentration** (µmol/l)	*Outpatient level* (µmol/l)
1	Twice	8·0	5·9, 15·7†
2	Twice	8·8	6·2
3	Thrice	13·6	12·3
4	Twice	12·4	7·6
5	Twice	12·6	8·4

*Steady-state saliva carbamazepine concentrations.
†Two levels determined one month apart.
Conversion given in footnote to Table 1.

taken in obtaining samples and interpreting their values in the period shortly after drug administration. Saliva concentration profiles are a convenient and effective means of assessing CBZ dose regimens in individuals, and it may be possible to use a similar approach for other anticonvulsant drugs.

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Osteoid osteoma and benign osteoblastoma in childhood

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SUMMARY Three cases of osteoid osteoma and one of benign osteoblastoma in children are described. The main complaint was severe pain which was worse at night; it was relieved by aspirin or other analgesics. The diagnosis was made on clinical and radiological grounds and was confirmed on histological examination of the central nidus removed at operation. The pain was relieved in the patients with osteoid osteoma, and it was very much less after operative removal of the benign osteoblastoma. Both conditions are probably variations of the same disease process, depending on the anatomical site and the type of bone affected.

Osteoid osteoma was described as a clinical entity in 1935 by Jaffe, and then more fully by Jaffe and Lichtenstein (1940). In 1932 Jaffe and Mayer reported a patient in whom the disease differed somewhat from osteoid osteoma, and Dahlin and Johnson (1954) further described such cases and used the term 'giant osteoid osteoma'. The term benign osteoblastoma was introduced by Jaffe (1956) and Lichtenstein (1956) independently to differentiate this condition from osteoid osteoma. Since then numerous reports on both conditions have appeared, mainly in orthopaedic and radiology journals. In our experience children with these conditions are referred about equally to general paediatric and orthopaedic clinics. Nevertheless the clinical picture, which is similar in both osteoid osteoma and benign osteoblastoma, appears to be unfamiliar to many paediatricians. It was for this reason, and also because of the inherent difficulty in making the diagnosis, that we describe our experience with three patients with osteoid osteoma and one with benign osteoblastoma seen in Sheffield during the last 12 years.

Case reports

Case 1. Osteoid osteoma, left femur. This boy was born on 2 October 1958 and was first seen at the orthopaedic clinic at age 7½ years with a history of pain in the left thigh and a limp for a year. The pain was not constant and was relieved by aspirin. An *x*-ray showed irregular sclerosis of the medial side of the upper half of the shaft of the left femur; there was a faint oval translucent area at the level of the lesser trochanter, which was confirmed on tomography. A radiological diagnosis of osteoid osteoma was made (Fig. 1).

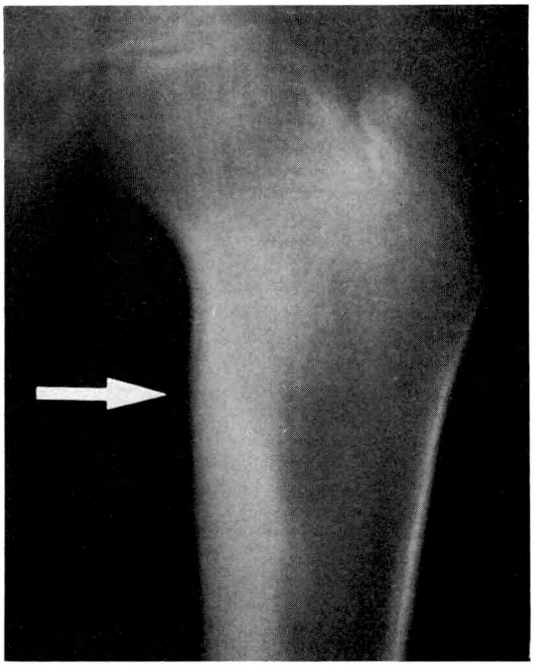

Fig. 1 *Case 1. Osteoid osteoma: sclerosis of medial side of femoral shaft and faint oval translucency at level of lesser trochanter.*

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A small piece of bone was removed from the upper part of the femur but this did not show any histological evidence of osteoid osteoma. The pain was relieved for a short time but returned when he started walking. Two months later, further *x*-rays showed that the lucent area was still present; the pain was now very severe. At age 8 years he was readmitted for observation but did not appear to have any pain. One month later he was having to take 'up to 3 aspirins' daily. Further *x*-rays and tomography again suggested osteoid osteoma, and the femur was explored; this was nearly one year after his first visit to the hospital and 2 years after the onset of symptoms. On this occasion several fragments of bone were removed. One of these contained a nidus of irregular, partially calcified osteoid trabeculae separated by loose vascular connective tissue containing osteoblasts and osteoclasts, and bounded by dense lamellar bone. The appearance was consistent with the clinical diagnosis of osteoid osteoma. After this operation the boy was free from pain.

He remained well until October 1973, when at age 15 years, he complained of being always tired; he was very pale. Hb was 7·6 g/dl and blood film showed pronounced iron deficiency anaemia. He admitted that he had taken aspirin since his original trouble and that he was now taking it for headaches. His urine showed a faint purple coloration with Phenistix, and plasma salicylate level was 6 mg/100 ml (0·43 mmol/l). He was readmitted (J.A.B.) for further investigation. Apart from extreme pallor, no abnormality was found except that his stools showed a positive result in a test for occult blood. Barium swallow and follow-through radiological examination were normal. He was given ferrous sulphate tablets and returned home. Six weeks later Hb was 11 g/dl; the ferrous sulphate was finally stopped 3 weeks later when Hb was 13·8 g/dl. He felt well; there was no wasting of the thigh, and knee and ankle jerks were normal on both sides.

This case shows how difficult it is to localise the lesion at operation, in spite of clear radiological evidence of its existence. Aspirin dependence is a hazard to which people with osteoid osteoma are particularly prone, and there is no doubt that taking aspirin regularly for a long period caused severe iron deficiency anaemia from gastrointestinal bleeding.

Case 2. Osteoid osteoma, right femur. This boy was born on 18 March 1962 and referred to one of us (J.A.B.) at age 10 years with a 4-month history of pain in the right leg. The pain was not continuously severe but was worse at night, waking him at about 2 a.m.; it was relieved by aspirin and he had been taking one tablet each night for the previous 2 months. He had also been noted to limp occasionally and for one month his right leg had been getting thinner.

There was 2·5 cm of wasting of the muscles in the right midthigh, and knee and ankle jerks were reduced on the right side; there was also slight wasting of the right gluteal muscles. No muscle weakness or sensory loss was detected. A lumbar puncture showed no evidence of block, and the CSF was normal. The only radiological abnormality was a thickening of the cortex at the level of the lesser trochanter (Fig. 2).

He was referred to the orthopaedic department (W.J.W.S.); there was some tenderness of the upper half of the right femur and further *x*-rays of the femur with different degrees of rotation confirmed the cortical thickening in the upper half of the shaft; there was no evidence of a lucent central lesion after tomography, but osteoid osteoma was considered likely. He was readmitted to hospital and a block of bone at the site of the cortical thickening was removed. The tissue contained a central lesion which was histologically similar to that described in Case 1 and was typical of an osteoid osteoma; his pain was completely relieved. The total duration between the onset of symptoms and operation was 8 months. 10 months after the operation he was free

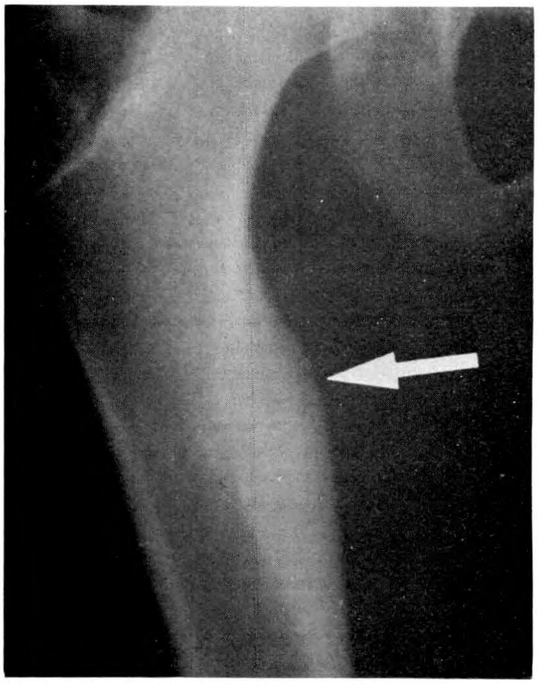

Fig. 2 *Case 2. Osteoid osteoma: sclerosis and thickening of the cortex at level of lesser trochanter.*

of symptoms; there was no wasting of the thigh, and his knee and ankle jerks on the right side were normal.

The wasting and reduced reflexes at first suggested a neurological lesion, but the radiological evidence strongly suggested an osteoid osteoma although a lucent area was never detected by radiography.

Case 3. Osteoid osteoma, left tibia. This girl was born on 24 October 1964 and referred at age 4½ years. She complained of a cramp-like pain in the left leg and a limp for the previous 2 months. The pain was particularly severe at night and was relieved by aspirin. There was slight wasting (2 cm) of the left thigh and calf muscles, with diminished muscle power in the left leg. The left ankle jerk was slightly diminished compared with the right side. *X*-rays showed cortical thickening of the posterolateral aspect of the lower tibial shaft (Fig. 3). There was a small lucent area which appeared to be deep to the sclerosis, and the diagnosis of osteoid osteoma was suggested.

She was admitted in May 1969 and at operation, using radio-opaque markers, a typical osteoid osteoma was removed; the diagnosis was confirmed histologically. The pain was completely relieved.

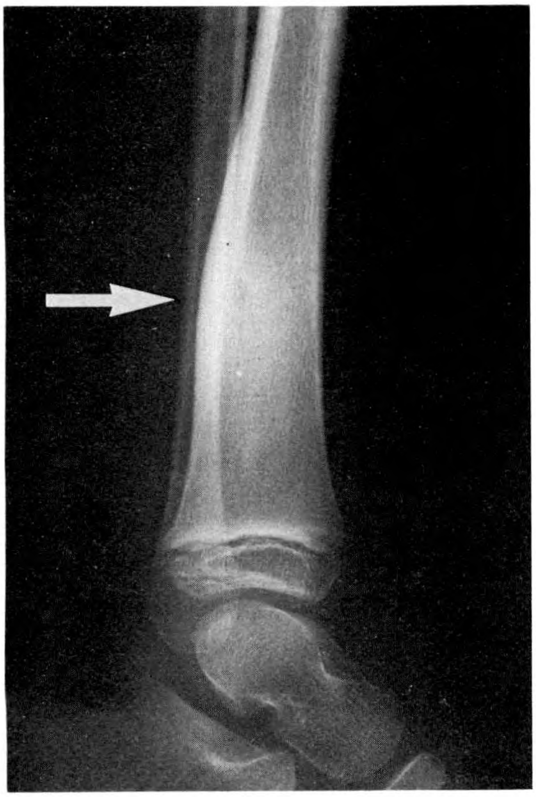

Fig. 3 *Case 3. Osteoid osteoma: sclerosis and thickening of the posterolateral part of the cortex of left tibia, with a small translucent area.*

Case 4. Benign osteoblastoma, right ischium. This boy was born on 4 December 1958 and, apart from lobar pneumonia at age 11 years, he had been well until he developed an aching pain in his right upper thigh at 13 years. He was seen at a paediatric outpatient clinic (J.A.B.) and was found to have 2 cm of wasting of the right thigh and 1·5 cm of wasting of the calf, with diminished knee and ankle jerks on the right side; there was a doubtful area of reduced sensation to pin pricks on the front of the right thigh.

Because of the possibility of compression of the right femoral nerve an IV urogram was done which showed an indentation of the bladder by a soft-tissue mass on the right side of the pelvis, and some sclerosis and thickening of the right ischium (Fig. 4). The ESR was 21 and 48 mm/in 1st hour. The right side of the pelvis was explored by an anterior approach; the right levator ani was bulkier than normal. A small piece of bone removed at operation showed no abnormality. The pain remained unchanged and he started taking paracetamol to relieve it. After 6 months' observation as an outpatient there was no improvement and he became a thin worried boy. He was referred to orthopaedic outpatients department (W.J.W.S.) where further *x*-rays, including tomograms, showed an area (1·5 cm in diameter) of lucency in the upper part of the right ischium. A Brodie's abscess was considered probable. He was readmitted and at exploration of the ischium an area of soft bone was scooped out. The histological appearance of the tissue removed was similar to that described in Case 1, except that the connective tissue separating the osteoid trabeculae was somewhat less vascular.

After operation his pain was almost completely relieved. He was last seen in 1973 (aged 14·8 years) when he still complained of slight pain: there was now only 0·6 cm of wasting of the right thigh, and knee and ankle jerks were equal on both sides. He was a cheerful boy and had gained 8 kg since the operation.

Discussion

Osteoid osteoma is twice as common in boys as in girls, with a maximum age incidence of between 10 and 25 years, and extremes from 1½ and 60 years (Poulsen, 1969). The presenting symptom is pain which is sometimes intermittent at first but later becomes continuous. The pain may vary in intensity and is characteristically worse at night. It has been

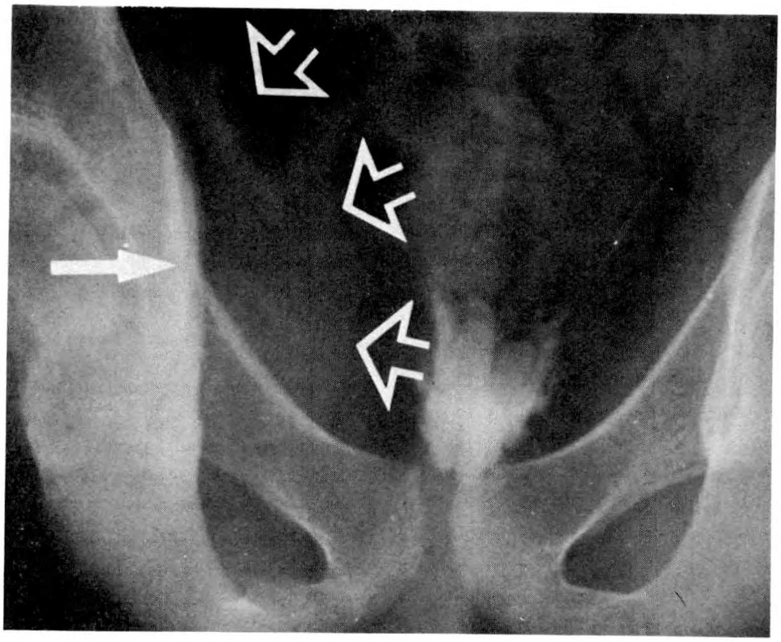

Fig. 4 *Case 4. Osteoblastoma: intravenous urogram showing indentation of bladder on right side (open arrows) with sclerosis and thickening of ischium.*

described as aching or boring, and patients usually obtain relief from such drugs as aspirin; this may cause dependence upon them (Case 1). Localisation is usually easy if a long bone is affected, but difficult if the lesion is in the upper part of the femur, the pelvis, or a vertebra. In order of frequency, the tibia and femur are most commonly involved, followed by the tarsal phalanges and the vertebrae, but almost any bone can be affected with the possible exception of the maxilla and facial bones. Lesions in the mandible (Flaherty *et al.*, 1956) and skull (Munk *et al.*, 1960) are rare. Epiphyseal lesions are rare but Sherman (1947b) described a patient with a lesion in the epiphysis of the great trochanter. Occasionally the pain is referred from the lumbar spine to the abdomen or leg, from the lesser trochanter to the knee, or proximally from the tibia to the hip (Golding, 1954), or thigh (Vaughan-Jackson, 1950). Very rarely the lesion is painless and presents as a swelling (Lawrie *et al.*, 1970). Other symptoms depend on the site of the lesion; if the shaft of the femur or tibia is affected there may be a limp, with wasting of muscles of the thigh, accompanied by loss or depression of knee and ankle jerks (Cases 1, 2, and 3). Rushton *et al.* (1955) found a positive Lasègue's sign in two cases with lesions of the femoral shaft, and one patient with loss of sensation to pain and touch over the anterolateral part of the thigh. Vertebral lesions may cause scoliosis, particularly in children and adolescents (Freiberger, 1960; Poulsen, 1969). In lesions near the elbow joint there is loss of flexion and extension with preservation of pronation and supination, and osteomyelitis may be suspected (Marcove and Freiberger, 1960). Szepesi *et al.* (1972) described two children with lesions in the great trochanter and femoral neck who had flexion contractures at the hip joints, and Johnson (1955) reported two patients with intracapsular lesions of the femoral neck in whom there was a chronic synovitis with fluid in the joints and infiltration of the synovial membranes with round cells. In young children deformity caused by uneven bone growth may develop if the lesion is near an epiphyseal plate (Ponseti and Barta, 1947), and in some cases the affected limb is longer than the normal one. Physical signs are varied; wasting rarely occurs except in the thigh or calf but a clinically evident effusion into an adjacent joint has been described (Sherman, 1947a; Spence and Lloyd-Roberts, 1961) and, particularly at the wrist and ankle, a nearby bone may show hyperostosis (Morton and Bartlett, 1966) or osteoporosis. Locally there may be exquisite tenderness and a slight increase in temperature. In areas easily accessible to palpation, thickening of the bone may be detectable. When a terminal phalanx is affected the whole finger end is swollen and dusky red, with excessive sweating and hypertrophy of the nail, and premature fusion of the phalangeal epiphyses has been observed (Rosborough, 1966). A lesion in a metatarsal bone may be mistaken for a march fracture (Kallio, 1963).

The clinical diagnosis of osteoid osteoma is notoriously difficult; the interval between the onset of symptoms and a correct diagnosis is seldom less than 6 months and it may be many years; it is not surprising, particularly in adults, that the depression, insomnia, and loss of weight produced by the long-continued pain often result in a diagnosis of hysteria or psychoneurosis. A limp, with wasting and reduced, or absent, knee and ankle jerks, may suggest compression of the femoral nerve or lumbosacral plexus, a cord lesion, or protrusion of an intervertebral disc. Brodie's abscess (Szepesi *et al.*, 1972) may be considered on clinical and radiological grounds, particularly if the sedimentation rate is slightly raised, which can occur in osteoid osteoma. O'Hara *et al.* (1975) considered that Brodie's abscess and stress fracture of the tibia were likely to cause the greatest diagnostic difficulties. Other conditions which may have to be considered (Purcell *et al.*, 1952) are solitary cortical abscess of bone, chronic sclerosing osteomyelitis of Garré, solitary tuberculous lesion in the shaft of a long bone, Ewing's tumour or osteogenic sarcoma, and chronic synovitis in cases with an effusion into an adjacent joint. A central cavity does not occur in chronic sclerosing osteomyelitis, but is found in a chronic tuberculous lesion. In case of doubt culture of material from the central lesion and microscopical examination should settle the diagnosis. The two malignant bone tumours can usually be distinguished by their rapid progression and destruction of bone. Lindbom *et al.* (1960) and O'Hara *et al.* (1975) have shown by angiography that the central area of an osteoid osteoma is extremely vascular, while a Brodie's abscess has an avascular centre.

Radiologically the lesion can usually be seen as a well-defined area of dense sclerosis, with a diameter of $\frac{1}{2}$–1 cm, occasionally up to 2 cm. In the centre of the sclerosis is a lucent nidus, sometimes containing speckled areas of calcification which may be mistaken for sequestra (Munk *et al.*, 1960).

Tomography may be necessary to demonstrate the central lesion, particularly if there is a considerable amount of thickened sclerotic bone surrounding it and, in some cases, a central area cannot be defined at all (Case 2). If the lesion is near the surface of the cortex or just under the periosteum, the long bones, especially the cortical bone, will be much thickened. Conversely, thickening is less pronounced if the lesion is in spongy bone. The thickened cortical bone can easily be missed unless a number of views are taken with different degrees of rotation (Case 2). Purcell *et al.* (1952) pointed out that thickened layers of subperiosteal bone may produce an 'onion peel' appearance similar to that seen in Ewing's tumour.

Spontaneous cure may occur after many years (Vickers *et al.*, 1959) and increased calcification in the central area has been regarded as evidence of healing (Moberg, 1951; Golding, 1954). However, the only effective treatment is complete excision of the whole central lesion. Accurate localisation of the lucent central area at operation is often difficult and may require the placing of markers under radiological control. In most instances the removal of a block of bone surrounding the actual lesion is preferable to an attempt to shell out the nidus as a small piece of tissue may be left behind; packing with an autogenous bone graft is sometimes required. Incomplete removal is followed by a recurrence of pain which can be relieved only by a further operation. Other methods of treatment, including radiotherapy, are useless.

Histologically the central lesion consists of an area of highly vascular tissue with wide vascular spaces and thick-walled blood vessels. There is much osteoid tissue, in irregular seams, with numerous osteoblasts. Unmyelinated nerve fibres have been found in the central area (Chandler and Kaell, 1950; Sherman and McFarland, 1965; Byers, 1968; Schulman and Dorfman, 1970), mainly in relation to the blood vessels. The aetiology of osteoid osteoma is obscure. Trauma seems to play a part in some cases (Marcove and Freiberger, 1960; Rosborough, 1966), particularly in the phalanges. The cause of the pain is not fully understood, but Golding (1954) showed that the pain in a metacarpal lesion could be relieved by applying a pneumatic tourniquet, inflated above the systolic pressure, to the upper arm. Sherman and McFarland (1965) pointed out that bone itself is relatively insensitive to pain and that bone lesions normally cause pain only when the periosteum is affected. Osteoid osteoma, however, is painful right from the start, irrespective of its anatomical relationship to the periosteum. Sherman and McFarland suggested that the unmyelinated fibres found in the lesions are autonomic nerves which are stimulated by distension of the blood vessels, causing pain and also the vascular dilatation and sweating which have sometimes been noted (Chandler and Kaell, 1960; Rosborough, 1966). The cause of the muscle wasting and depression of reflexes is difficult to explain as the weakness of the affected muscles is slight and certainly not sufficient to affect the reflexes: nor in most cases is there any significant amount of disuse of the affected limb. The vascular symptoms are similar to those found in glomus tumours (Kohout and Stout, 1961; Laymon and Peterson, 1965) in which there is sometimes vasodilatation and increased sweating of an affected finger (Stabins *et al.*, 1937) similar to that seen in a few cases of osteoid osteoma.

Benign osteoblastoma was differentiated from osteoid osteoma by Dahlin and Johnson (1954) who at first used the term giant osteoid osteoma. In 1964 Lichtenstein and Sawyer reviewed reports and added a number of new cases. The age, sex incidence, and distribution of lesions in benign osteoblastoma are similar to those of osteoid osteoma, but the former occurs more often in spongy than in cortical bone. Pain is less severe than in osteoid osteoma and is less easily located. The lesion is generally larger (2·5–5 cm in diameter), less regular in shape, and there is more thickening of the surrounding soft tissue (Case 4). When a vertebra is affected there may be compression of the cord or roots (Lichtenstein and Sawyer, 1964). Radiologically, there is an expanding area of bone destruction, usually with a sclerotic margin; when the surrounding bone is perforated a soft tissue mass is formed which may be identifiable in *x*-rays (Case 4). The differential diagnosis is similar to that of osteoid osteoma but should also include giant-cell tumour, fibrous dysplasia, aneurysmal bone cyst, nonossifying bone fibroma, and eosinophil granuloma (Wellmer *et al.*, 1968). Angiography may be helpful in difficult cases, as in osteoid osteoma. Treatment is by excision. In benign osteoblastoma the osteoid tissue is less regularly arranged than in osteoid osteoma and there are more multinucleated cells in addition to the osteoblasts. It remains uncertain, however, whether the two conditions are completely separate or are variations of the same disease process. A third, apparently related condition with multiple lesions similar to osteoid osteoma has also been described (Schajowicz and Lemos, 1970). De Souza Dias and Frost (1974) regard all three conditions as osteoblastoma and suggest a classification according to site: cortical osteoblastoma, spongious osteoblastoma, periosteal osteoblastoma, and multifocal osteoblastoma. They considered that the radiological appearance depended on the site of the lesion; in compact bone in or near cortex (osteoid osteoma) there was considerable tissue reaction, while in spongy bone (osteoblastoma) there was relatively little reaction. Schajowicz and Lemos (1970) also pointed out that an insistence that these lesions are always benign is probably unjustified in our present state of knowledge.

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The following articles will appear in future issues of this journal:

Juvenile diabetes mellitus. The possibility of prevention. *J. W. Farquhar.*

Effective treatment for rhinopulmonary mucormycosis in a boy with leukaemia. *O. B. Eden and J. Santos.*

Mycoplasma pneumoniae infection. A follow-up study of 50 children with respiratory illness. *J. Y. Q. Mok, P. R. Waugh, and H. Simpson.*

Critical assessment of small bowel biopsy in children. *J. F. T. Glasgow, C. W. B. Corkey, and A. Molla.*

Neutrophil function in children with acute lymphoblastic leukaemia in the presence and absence of viral infections. *M. M. Reid, A. W. Craft, and W. T. Low.*

Status asthmaticus in children. A one-year study. *S. A. McKenzie, A. T. Edmunds, and S. Godfrey.*

Archives of Disease in Childhood, 1979, **54**, 466–468

Cushing's disease presenting with growth failure: clinical remission during cyproheptadine therapy

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SUMMARY A 14·7 year-old boy had almost complete suppression of growth as a result of mild pituitary-dependent Cushing's disease. There was complete clinical remission during treatment with cyproheptadine (12 mg/day) and this was maintained when treatment was stopped after 18 months.

There have been several reports of children with Cushing's disease in which the salient clinical feature has been retardation of growth (Copinschi *et al.*, 1969; Streeten *et al.*, 1975; Lee *et al.*, 1975; Solomon and Schoen, 1976). Such a patient is described who underwent complete clinical remission during treatment with the serotonin-antagonist cyproheptadine.

Case report

Clinical features. The patient was first seen at age 14·7 years because he had not grown during the previous 4 years. His parents had kept a record of his heights from age 1½ years, and this showed fairly abrupt cessation of growth between ages 10 and 11 (Fig. 1). At about this time he gained weight rather quickly and his appearance changed as his face became rounder. Pubic hair appeared at about 11 years but there was no further progression in pubertal development.

When he was 6 years he had a successful course of treatment with gonadotrophin for an undescended testis, and a hydatid of Morgagni was excised when he was 10. In all other respects his health had been normal and he had no other symptoms.

On examination he was short (142·3 cm) and slightly obese (40·4 kg), with a round face (Fig. 2). With the exception of moderate hypertension (BP 135/95 mmHg), and slight bilateral gynaecomastia with mild generalised hirsutism, there were no other abnormal findings. His testes were prepubertal (1–2 ml), but he had a moderate amount of pubic hair with some development of the penis and scrotum.

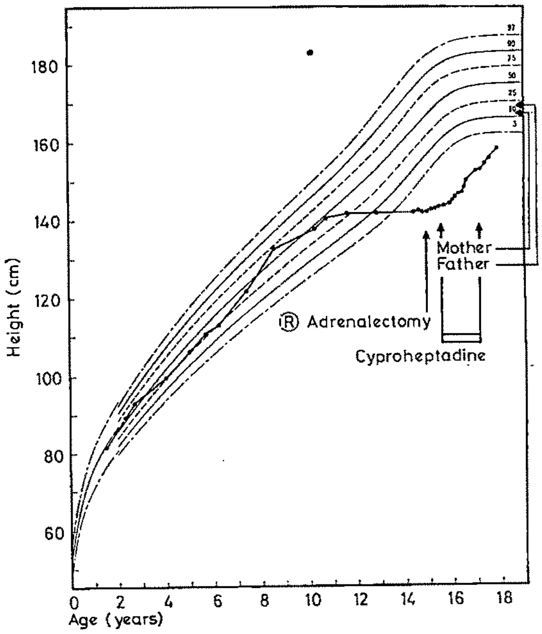

Fig. 1 *Patient's growth curve between ages 1½ and 18 years. Heights of his parents are also shown. Arrows show the timing of adrenalectomy and cyproheptadine therapy.*

Laboratory investigations. The initial investigations confirmed the clinical diagnosis of mild Cushing's disease. Urine free-cortisol was high at 565 nmol/24h

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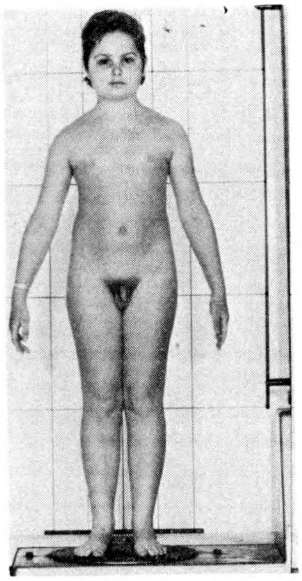

Fig. 2 *Appearance of the patient at age 14·7 years.*

(20·5 μg/24h), urine 17-hydroxycorticoid excretion was 82 μmol/24h (23·6 mg/24h), the cortisol production rate was raised at 83 μmol/m^2 per 24h; 30·6 mg/m^2 per 24h (normal 34·5 ± 7·9 SD), and the urine 17-oxosteroids were high at 44 μmol/24h (12·7 mg/24h). Plasma cortisol showed loss of normal circadian variation (260 nmol/l; 9·4 μg/100 ml at 0900h; 364 nmol/l; 13·1 μg/100 ml at 2300h). After 3 days' treatment with high-dose dexamethasone (2 mg 6-hourly) urine 17-hydroxycorticoids fell to 5·6 μmol/24h (1·6 mg/24h) and the 17-oxosteroids to 22.4 μmol/24h (6·4 mg/24h). However, plasma ACTH was undetectable (<32 ng/l) at times when the plasma cortisol ranged between 340 and 660 nmol/l (12·3 and 24 μg/100 ml). In view of the last finding, an adrenal tumour was suspected and an iodocholesterol scan was carried out. This showed apparently normal uptake by both adrenal glands, thus excluding the presence of a tumour.

Other endocrine causes of growth failure could be readily excluded. Plasma growth hormone rose from <1·0 to 25·4 mU/l 20 minutes after IV injection of 0·1 U/kg insulin. Plasma cortisol rose from 460 to 725 nmol/l (16·7 to 26·3 μg/100 ml) during this test. Plasma thyroxine was normal (121 nmol/l; 9·4 μg/100 ml), but a subsequent test with IV TRH (200 μg) showed an insignificant rise in plasma TSH from 1·0 to 1·6 mU/l after 30 minutes. Basal prolactin was normal (112 mU/l) and rose normally to 300 mU/l 15 minutes after TRH.

X-ray of the left wrist and hand showed a bone age of 11·4 years (Tanner *et al.*, 1975). Skull *x*-rays and IV-urogram were normal.

Clinical course. Two-stage adrenalectomy was planned and the right adrenal was removed when the patient was aged 15·1 years. The gland appeared normal in size (weight 6 g) and there was no evidence of hyperplasia on histological examination. In view of these findings, left adrenalectomy was deferred, and his adrenal function was reassessed after 2 months. Again, high urine free-cortisol levels were obtained (350–675 nmol 24h; 127–245 μg/24h). Serial estimation of plasma cortisol suggested episodic activity of his Cushing's disease. On one particular day, plasma cortisol varied from 860 nmol/l (31·2 μg/100 ml) at 0900 hours to 440 nmol/l (15·9 μg/100 ml) at 2300 hours, but the next day the levels were almost normal—280 nmol/l (10·1 μg/100 ml) at 0900 hours; 113 nmol/l (4·1 μg/100 ml) at 2300 hours. On both days plasma ACTH was low to normal (<22–58 ng/l).

During the next 6 months he grew very little and there was no appreciable advance in his bone maturation or pubertal development. When he was 15·8 years old, his height was 144·3 cm, and treatment with cyproheptadine (12 mg/day) was started. During the next 4 months he grew 1·2 cm, and after 6 months there was a definite increase in testicular size and his BP had fallen to 110/70 mmHg. At this time, normal values for plasma cortisol were found (80–225 nmol/l; 2·9–8·1 μg/100 ml) and his urine free-cortisol fell to 180–300 nmol/24h (65–109 μg/24h). A year after starting cyproheptadine his bone age was 12·6 years.

Treatment with cyproheptadine was stopped after 18 months when he was 17·3 years old. At this time his height was 153·7 cm, blood pressure 125/65 mmHg, further pubertal development had taken place (testicular volume 16–20 ml), and his gynaecomastia was unchanged. He has been followed up for 9 months since stopping cyproheptadine and has continued to grow normally without gaining weight; at age 18 years his height was 158·5 cm, his weight 45 kg, and his bone age 14·9 years. Urine free-cortisol levels have remained normal (90–182 nmol/24h; 33–66 μg/24h) since stopping treatment. Plasma cortisol estimated 3 months after stopping cyproheptadine showed very similar morning and late evening values: 210–300 nmol/l (7·6–10·9 μg/100 ml) at 0900 hours and 275–290 nmol/l (10–10·5 μg/100 ml) at 2200 hours, but 6 months later normal circadian variation appeared to be present: 240 nmol/l (8·7 μg/100 ml) at 0900 hours; 120 nmol/l (4·3 μg/100 ml) at 2200 hours.

Discussion

It is well known that excess secretion of cortisol in Cushing's disease greatly suppresses growth but only recently has it been widely appreciated that in some patients the disorder may be mild and, apart from growth retardation, there may be few of the classic clinical features (Lee *et al.*, 1975; Solomon and Schoen, 1976). In this case, there was some evidence that the disorder was episodic, as shown by the plasma cortisol profiles on two consecutive days. Plasma ACTH was at no time raised and at times it was undetectable, an unusual finding in pituitary-dependent Cushing's disease. Both these findings are probably in keeping with the observation that the resected right adrenal gland was normal in size and showed no histological evidence of hyperplasia. In the case reported by Lee *et al.* (1975), the adrenal glands were also normal on histological examination.

Our patient's normal growth hormone (GH) secretion is also unusual, as patients with Cushing's disease almost invariably have suppressed GH secretion (Copinschi *et al.*, 1969; Streeten *et al.*, 1975). This probably reflects the mildness of his disorder, as it appears that suppression of GH is largely related to high levels of plasma cortisol, rather than being due to a primary disturbance of hypothalamic or pituitary function (Tyrrell *et al.*, 1977).

In nearly all previously reported cases, patients with Cushing's disease presenting with growth failure were treated by bilateral adrenalectomy, and this was planned in our patient. Such treatment results in renewed growth but commits the patient to life-long replacement therapy with corticosteroids. There is also a significant risk that Nelson's syndrome (pituitary adenoma with hyperpigmentation) will develop later. Pituitary irradiation (Jennings *et al.*, 1977), or trans-sphenoidal exploration of the pituitary to remove an ACTH-secreting microadenoma (Tyrrell *et al.*, 1978), have also been successful in children with Cushing's disease.

As the disorder was mild in our patient a trial of cyproheptadine was given. This drug, which antagonises the effects of serotonin and suppresses ACTH secretion in normal subjects (Plonk and Feldman, 1976), was used successfully by Krieger *et al.* (1975) in the management of three adults with Cushing's disease. So far the use of this drug in children with Cushing's disease has been disappointing (Allgrove *et al.*, 1977; D'Ercole *et al.*, 1977), but in our case its use was associated with a pronounced acceleration of growth and bone maturation, and remission of hypertension. Spontaneous remission has been described in children with Cushing's disease (Putnam *et al.*, 1972) and this could account for our patient's improvement during treatment. However, we believe that a trial of cyproheptadine is indicated as the first line of treatment in patients with relatively mild Cushing's disease.

We thank Professor J. M. Tanner for referring the patient, Dr Lesley Rees for assistance with the ACTH assays, and Dr M. Savage for the bone-age estimations.

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Short reports

Rectal paracetamol in small children with fever

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SUMMARY 37 febrile children aged between 3 months and 6 years were treated with paracetamol in a dose of 15–20 mg/kg by either oral elixir or rectal suppository. The rectal route was found to have an equal antipyretic effect and offers a practical alternative in those children for whom the oral route is not possible.

A high fever in a small child brings the risk of a convulsion as well as causing discomfort and increasing fluid loss. It has been shown that antipyretic drugs cool better than mechanical methods (Hunter, 1973), and that paracetamol and acetylsalicylate are equally effective (Colgan and Mintz, 1957; Eden and Kaufman, 1967). Paracetamol is often preferred because it has fewer adverse effects in therapeutic dosage and because accidental poisoning is less likely. The oral route is sometimes impractical—for example in a child who is convulsing, comatose, or vomiting—and absorption after oral ingestion may be impaired by the delay in gastric emptying that accompanies a severe illness (Heading *et al.*, 1973). At present no parenteral form of paracetamol is available. Previous work shows that paracetamol in rectal suppositories is well absorbed, but at a dosage of 10 mg/kg reduces fever in children less effectively than an oral elixir (Keinänen *et al.*, 1977). We therefore compared the antipyretic effect and practicability of the oral and rectal routes in small children using paracetamol in higher dosage.

Patients and method

40 children with rectal temperatures of at least 38·5°C were divided into two age groups (between 3 months and 2 years, and between 2 and 6 years) and randomly allocated within each group to either oral or rectal paracetamol. The oral preparation was the standard BPC elixir containing paracetamol 120 mg/5 ml, and the suppositories, which were made up in the hospital pharmacy, contained paracetamol 120 mg or 240 mg in 1 g of triglyceride base (Witepsol H15). Each child was given a single dose of 15 mg/kg paracetamol rounded to an appropriate multiple of 120 mg. Mean dosages ± 1 SD in the younger children were 20·2 ± 3·8 mg/kg (oral) and 19·7 ± 3·0 mg/kg (rectal), and in the older group 16·3 ± 3·3 mg/kg (oral) and 17·8 ± 2·4 mg/kg (rectal) (differences between dosages within each group were not statistically significant). Difficulties in drug administration were noted. Conditions were standardised as much as possible: the only clothing was nappies or pants, oral fluids were encouraged if appropriate, but no other means of cooling were used. The ambient temperature, which was monitored throughout the study period, was similar for each group of children. Rectal temperatures were recorded every 15 minutes for 3 hours by the same observer using an electric thermometer (IVAC 821).

Among the younger children, in the oral group 6 had upper respiratory tract infection (URTI), 3 bronchiolitis, 1 gastroenteritis, 1 mumps, and 1 encephalitis; in the rectal group 7 had URTI, 2 gastroenteritis, 1 bronchiolitis, 1 pneumonia, 1 urinary tract infection, and 1 encephalitis. Among the older children, in the oral group 5 had URTI, 1 mumps, 1 urinary tract infection, and 1 pyrexia of unknown origin; in the rectal group 4 had URTI, 1 measles, 1 cervical adenitis, and 1 roseola infantum. The groups were comparable in respect of duration of illness, state of hydration, and concurrent therapy, all these factors being recorded. The 2 children with encephalitis exhibited resistant hyperpyrexia and were therefore excluded from analysis, as was a third child in the younger oral group, who was found to have been given an extra dose of paracetamol in error. Paracetamol could not be given orally to 2 of the children initially allocated to this route, one because of vomiting and the other because of a convulsion; their inclusion in the rectal group did not bias the initial mean temperatures. There was no difficulty in giving the suppositories, even in children who had diarrhoea. One child (included in the analysis) extruded a partly-dissolved suppository 2 hours after its insertion.

Results

18 children (10 under 2, and 8 between 2 and 6 years) received oral paracetamol and 19 children (12 under 2, and 7 between 2 and 6 years) received rectal paracetamol. The initial mean temperatures of the younger children were 38·95°C (oral group) and 39·23°C (rectal group), and of the older children 38·89°C (oral group) and 38·99°C (rectal group). Within each age range the relationship between fall in temperature and time up to 3 hours from administration of paracetamol was highly significant ($P<0·001$) for both routes, and there was no significant difference between the routes. Figs 1 and 2 show the mean change from initial temperature at 15-min intervals in both age groups. Generally, the oral group of younger children cooled down more than the rectal group for most of the study period (Fig. 1), and the oral group of older children cooled down better at first but were later overtaken by the rectal group (Fig. 2); however these differences were not statistically significant. The mean fall in temperature of the younger children after 3 hours was 1·83°C (oral) and 1·66°C (rectal), and for the older children 1·63°C (oral) and 1·89°C (rectal) but there was a wider scatter in response among the rectal groups, possibly because of greater variability in absorption.

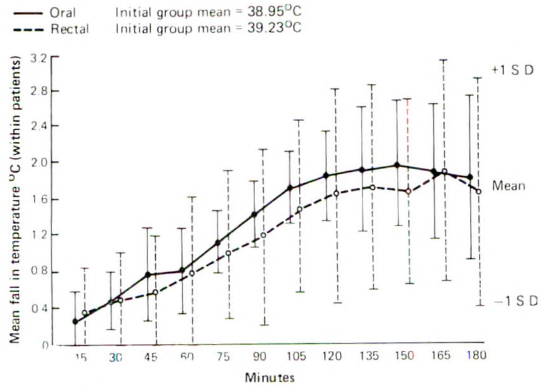

Fig. 1 *Mean change from initial temperature ± 1 SD at 15-min intervals for the children under 2 years on oral or rectal paracetamol.*

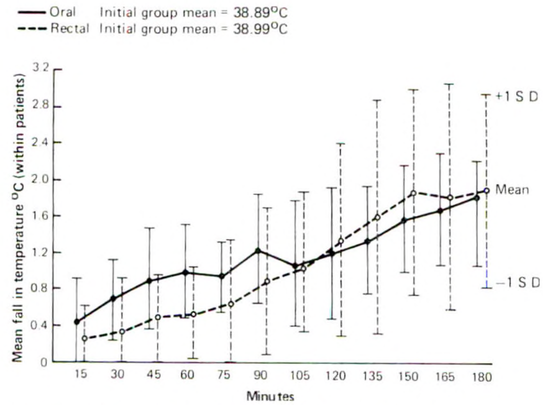

Fig. 2 *Mean change from initial temperature ± 1 SD at 15-min intervals for the children aged between 2 and 6 years on oral or rectal paracetamol.*

The younger children had generally reached their maximum fall in temperature by 150 minutes, whereas the temperatures of the older children, despite a smaller mean dosage of paracetamol, were usually still dropping at 180 minutes; this difference did not achieve statistical significance.

Discussion

Our results show that suppositories of paracetamol in small children in a dosage of 15–20 mg/kg offer an effective and practical alternative to an oral elixir. If both routes are available the oral may be preferred because of the greater consistency of response, but if oral administration is impossible the rectal route provides a good substitute. Paracetamol suppositories can be easily manufactured by a hospital pharmacy, but it would be helpful if they were widely available commercially so that they could be used at home. Their absorption characteristics may be improved if polyethylene glycol is used as base rather than triglyceride (Keinänen *et al.*, 1977).

We thank the Boots Drug Company whose grant made this study possible, IVAC (UK) for the electric thermometer, and our hospital pharmacy who made up the suppositories.

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Acute infantile thrombocytosis and vitamin K deficiency associated with intracranial haemorrhage

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SUMMARY A 5-week-old breast-fed girl presented unconscious and convulsing with heavily blood-stained CSF under increased pressure. This was associated with oozing from venepuncture sites, a grossly prolonged prothrombin time, and a raised platelet count. The prothrombin time became normal 18 hours after she had been given parenteral vitamin K and a transfusion of fresh plasma and red cells, but the thrombocytosis persisted. A moderate communicating hydrocephalus also remained and was treated, and one year later health and development appeared normal. The thrombocytosis resolved after a few weeks and has not recurred.

Thrombocytosis in infancy accompanying intracranial haemorrhage is rare and in the few cases that have been recorded was not associated with a clinical bleeding tendency or blood coagulation deficiency (Sanyal *et al.*, 1966).

We describe the case of a 5-week-old infant with an intraventricular haemorrhage who was found to have a high platelet count and was also noted to have a bleeding disorder with a grossly prolonged prothrombin time. This triad of intracranial bleeding, thrombocytosis, and possible late vitamin K deficiency has not been reported before.

Case report

The patient, the first child of healthy parents, was born after a normal pregnancy. The delivery was normal and her birthweight was 2·86 kg. Vitamin K was not given at birth. She was breast fed and in good health until age 5 weeks when she vomited and was irritable for 3 days, before becoming comatose. On admission to hospital she was unconscious, moaning, very pale, rigid, and had a tensely bulging anterior fontanelle. She also had two small bruises in the popliteal fossa and was seen to ooze excessively from venepuncture sites but there was no evidence of external injury.

Lumbar puncture showed blood-stained and markedly xanthochromic CSF under increased pressure. Subsequently, a ventricular tap also yielded heavily blood-stained CSF. Hb was 7·1 g/dl; WBC 14·3 × 10^9/l (differential counts showed a neutrophilia); and platelets 1154 × 10^9/l. The prothrombin time was grossly prolonged, as were partial thromboplastin and plasma recalcification times, but the thrombin time and concentration of fibrin/fibrinogen split products were normal.

Immediate transfusion of 50 ml fresh plasma and 90 ml stored blood was given together with 2 mg parenteral vitamin K; 18 hours later there was total correction of the prothrombin and recalcification times, with the partial thromboplastin time returning to normal in 42 hours. The platelet count, however, remained high at 900 × 10^9/l, and a further legacy of the event was a moderate, freely communicating hydrocephalus, which was treated with ventricular drainage and, subsequently, by isosorbide by mouth.

Platelet function studies were normal, and the thrombocytosis was last noted 4 weeks after presentation (760 × 10^9/l) but had disappeared 7 months later (340 × 10^9/l). The relevant haematological parameters are given in the Table.

Clinically the child has no apparent sequelae, and is well at the time of writing (2 years). Prothrombin time, partial thromboplastin time, and plasma recalcification time have apparently remained normal since correction after plasma and vitamin K on the one occasion, and the thrombocytosis has not recurred.

Table *Summary of haematological abnormalities after admission*

Time after admission	*Hb (g/dl)*	*Platelets (× 10^9/l)*	*Prothrombin time (British corrected ratio)*	*Partial thromboplastin time (ratio to control)*	*Fibrin degradation products (µg/ml)*
0	7·1	1154	>10·0	>10·0	<10
18 hours	11·1*	750	1·15†	1·4	—
42 hours	9·2	510	1·0	0·9	<10
4 days	10·2	900	—	—	—
13 days	10·4	1015	—	—	—
1 month	11·3	760	—	—	—
8 months	13·0	340	—	—	—

*After transfusion, †after vitamin K and fresh plasma.

Discussion

High platelet counts are rarely found in babies, and conditions associated with them have been reviewed (Addiego *et al.*, 1974). The thrombocytosis in this patient was discovered at the same time as a subarachnoid and intraventricular haemorrhage and a gross coagulopathy, and how these relate to each other is not certain. A likely sequence of events is that the coagulopathy allowed bleeding which provoked an unusually pronounced reactive platelet increase. If the high platelet count was the *cause* of bleeding, as paradoxically can occur in some myeloproliferative disorders, the coagulopathy would have to have been coincidental, which seems improbable.

Infantile central nervous system disease associated with thrombocytosis alone has been recorded by Sanyal *et al.* (1966) and Huttenlocher and Smith (1968) and has been implicated as being causally related (by precipitating cerebral thrombosis) as the high platelet count was seen to precede an acute hemiplegia in one case (Huttenlocher and Smith, 1968). In no previous report has a coincidental disorder of coagulation been noted.

Late vitamin K deficiency in infants has been described (Nammacher *et al.*, 1970; Cooper and Lynch, 1979), and while the evidence for its existence in our case is entirely circumstantial, it is hard to offer an alternative explanation for such rapid permanent *in vivo* correction of a clinically obvious bleeding tendency associated with a prolonged prothrombin time in the absence of intravascular coagulation. There was no reason to suppose that the production of liver coagulation factors was impaired from any other cause, but no estimation of protein induced by vitamin K absence was made, which would have helped to clarify this aspect.

Quite why this child should be lacking vitamin K is hard to say, as breast feeding is the only reason to suppose a deficient supply. It must be acknowledged that it is possible some other factor provided permanent correction of the observed and apparently acquired bleeding tendency, but to define such a factor is not possible.

We thank Dr B. L. Priestley for referring this infant to us.

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Premature menarche without other evidence of precocious puberty

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SUMMARY We describe 4 young girls with recurrent vaginal bleeding in the absence of other signs of precocious sexual development. Investigation showed low oestrogen levels in 2 of them, and basal gonadotrophins were in the upper part of the prepubertal range. We believe that the isolated early menstruation in these patients was possibly related to increased sensitivity of the endometrium to oestrogens.

Cyclical vaginal bleeding in the absence of other signs of secondary sexual development is rare and little has been written about the clinical and laboratory aspects of this condition. We describe 4 young girls seen at The Hospital for Sick Children because of recurrent menstrual bleeding; they had no other stigmata of precocious puberty or evidence of an underlying genital disorder.

Case reports

Case 1 (born 14.11.1960). When she was 10 months, this girl began to have episodes of vaginal bleeding which lasted for 2 or 3 days and recurred every 4 to 5 weeks. She had been born 2 weeks after the expected date of confinement, but her neonatal history and developmental progress were normal.

She was admitted to hospital at age 1·2 years for further investigation. Her height (80 cm) and weight (11·4 kg) were just above the 75th centiles. No abnormality was found on examination. In particular, there was no breast development or pubic hair, no abnormal skin pigmentation, and examination under anaesthesia (EUA) was normal with no adnexal masses. A vaginal smear taken at the time of bleeding showed immature epithelial cells, but a further smear taken 2 weeks later showed definite evidence of oestrogenisation. Bone age was appropriate for chronological age, the urine 17-oxosteroids were not raised (0·4 µmol/24h; 0·1 mg/24h), and a slight increase in urine gonadotrophins was found on bioassay (2·1 HMG 20A units/24h).

Vaginal bleeding continued fairly regularly until age 3·4 years and then it began to lessen, finally stopping at age 4½. Urine gonadotrophins were undetectable (<0·2 HMG 20A units/24h) when re-estimated by bioassay at age 3·2 years.

When she was 10·8 years, vaginal bleeding recurred and took place almost daily. Because of continued bleeding she was readmitted at age 11·3 years. At that time she had early breast development but no pubic hair. Her height and weight were on the 50th centiles, her bone age was slightly advanced (12·5 years), and a vaginal smear showed definite evidence of oestrogenisation. Urinary oestrogen excretion was in the early pubertal range (10·5 nmol/24h; 3 ng/24h), as was urinary luteinising hormone (LH) excretion (6·5 IU/24h). Skeletal survey showed no evidence of fibrous dysplasia.

At age 12·2 years, her menorrhagia stopped and her periods became more regular. Secondary sexual development proceeded normally. When last seen at age 14·3 her menses were regular, pubertal development was well advanced, and her growth appeared complete.

Case 2 (born 13.4.1973). This girl, who was born after a normal pregnancy, began to have vaginal bleeding when she was aged about 18 months. This occurred every 28 days and lasted for up to 7 days with occasional intermenstrual spotting. She complained of abdominal pain before the onset of each episode of bleeding, but was otherwise in good health.

She was admitted for investigation at age 3½ years. Her height (92·8 cm) and weight (13·4 kg) were on the 50th centiles. There was no palpable breast tissue or pubic hair, and the vulva appeared infantile. She had no abnormal skin pigmentation. Investigations showed that the bone age was slightly retarded (2 years) and no evidence of fibrous dysplasia was seen on *x*-rays of the skull and long bones. Urinary LH (2·9 IU/24h) and FSH (2·1 IU/24h) excretion were within the normal range for age, as were serum LH (2·0 mIU/l) and FSH (1·0 mIU/l). Plasma oestradiol was undetectable (<0·1 pmol/l; <0·03 pg/ml). EUA showed a small uterus with no adnexal masses, and cystoscopy was normal.

The patient had an episode of vaginal bleeding soon after the EUA, but when last seen at age 4·1 years there had been no further bleeding or other symptoms.

Case 3 (born 28.11.1974). This girl was seen when she was 2·9 years because of 7 episodes of vaginal bleeding since age 2·2 years. Her health and development until this had been normal. On examination, her height (89·6 cm) and weight (12·6 kg) were near the 50th centiles. No breast tissue was palpable and there was no pubic hair. The vulva appeared infantile and no pelvic masses were palpable on rectal examination. There was no abnormal pigmentation. Investigation at age 3·4 years showed a bone age between 3 and 3½ years and no evidence of fibrous dysplasia on skeletal survey. No hypothalamic or other brain abnormality was found on CAT. Her urinary LH excretion (1·1 IU/24h) and serum LH (1·0 mIU/l) were appropriate for her age, and there was no significant rise in serum LH after injection of 100 µg luteinising hormone-releasing hormone (LRH). In contrast, urinary FSH excretion was slightly raised (3·4 IU/24h) and after injection of LRH, there was a pronounced rise in serum FSH from 1·7 to 33·0 mIU/l after 60 minutes. Urinary total oestrogen excretion was 3·5 nmol/24h (1 ng/24h).

Case 4 (born 18.2.1975). This girl began having vaginal bleeding when she was 3 months; it occurred at intervals of between 30 and 32 days, lasted for 2 or 3 days, and was preceded by up to 10 days of irritability and feeding difficulties. She had been born 2 weeks after term, but her health and developmental progress had been normal. When she was older, she complained of abdominal pain before each episode of bleeding.

When she was 2 years she was admitted to another hospital where an EUA was normal. As her bleeding continued, she was referred to The Hospital for Sick Children for further investigation. When seen at age 2·9 years, her height (93·3 cm; 75th centile) and weight (13·4 kg; 50th centile) were normal. There was no breast development or pubic hair, and the vulva appeared infantile. Rectal examination was normal and there was no abnormal skin pigmentation.

Investigations showed a slightly retarded bone age (2 years), serum LH (2·8 mIU/l) and FSH (2·1 mIU/l) were in the upper prepubertal range. There

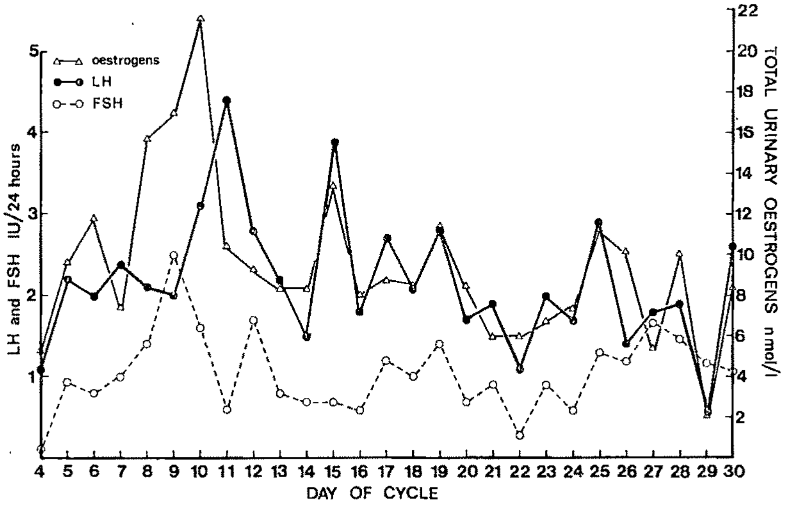

Figure *Urinary LH, FSH, and total oestrogen excretion from day 4 to 30 of a menstrual cycle (Case 4). A further episode of bleeding took place 7 days after the last collection of urine.*

Conversion: *SI to traditional units—urinary oestrogens: 1 nmol/l ≈ 0·27 ng/ml*

was no evidence of fibrous dysplasia on *x*-rays of the long bones.

Serial 24-hour collections of urine were carried out by the girl's mother at home. The collections were started on the 4th day after onset of bleeding and a further episode of bleeding took place 7 days after the collection period ended. The results for total urinary oestrogens, LH, and FSH excretion are shown in the Figure. While total urinary oestrogen excretion was generally low, an apparent peak of excretion took place on the 7th day of the collection (10th day of cycle). The next day, there appeared to be a small peak of LH excretion (4·3 IU/24h), with a possible further peak (3·9 IU/24h) 5 days later. Urinary FSH excretion was low throughout the period of collection.

Discussion

Our 4 cases are very similar to a case described by Blunck *et al.* (1967) in a review of transient sexual precocity. Their patient had recurrent menstrual bleeding which was not associated with other signs of secondary sexual development and she subsequently developed normally. In his textbook, Huffman (1968) described 2 such patients and referred to their benign clinical course. Similarly, our Case 1 menstruated fairly regularly between ages 10 months and 3·4 years and she subsequently had normal secondary sexual development after an initial period of menorrhagia. Our other 3 patients menstruated for between 1·2 and 2·7 years without other stigmata of precocious puberty, such as accelerated growth and bone maturation.

In a proportion of cases with precocious puberty, menstrual bleeding may be the first clinical manifestation. For example, Sigurjonsdottir and Hayles (1968) found that 5 out of 54 girls with precocious puberty presented with bleeding between ages 6 months and 1·9 years. Further evidence of secondary sexual development occurred within 2 months to 1·8 years.

Menstrual bleeding is often the first sign of precocious puberty in the McCune-Albright syndrome, in which it is associated with abnormal skin pigmentation and fibrous dysplasia of bone. While in none of our Cases 1–4 was there abnormal skin pigmentation, we have seen 2 girls with a forme-fruste of McCune-Albright syndrome and no abnormal skin pigmentation. The first of these girls started to menstruate at age 6 weeks and the second at age 5·9 years. Initial *x*-rays were normal in both girls and radiological evidence of fibrous dysplasia did not develop until ages 7 and 9 years respectively. It is therefore possible that fibrous dysplasia may later become apparent in Cases 1–4.

In at least one patient, a local genital lesion was initially suspected as the cause of vaginal bleeding. Although a vaginal foreign body may present with bleeding, this does not show the cyclic pattern described above and usually causes a purulent vaginal discharge, which was not present in any of our patients. Genital neoplasms—such as botryoid sarcoma or hormonally active ovarian tumours—are rare causes of vaginal bleeding in childhood and were excluded by physical examination in our patients. Ingestion of oestrogen was suspected as a cause of the bleeding, but this was denied by the girls' mothers. In addition, the episodic nature of the bleeding and the absence of breast development virtually exclude this possibility.

We have no good explanation for the early menstruation in our patients, but believe that it may be due to increased sensitivity of the endometrium to circulating levels of oestrogens which are too low to produce breast development. Certainly, the oestrogen values obtained in 2 of the patients were far below the levels found in normal ovulatory cycles. Case 4 apparently had a peak of urinary LH excretion on the 11th day of one of her menstrual cycles which was preceded by a peak of urinary oestrogen excretion on the previous day. The brisk rise in FSH after LRH stimulation in our Case 3 is surprising and is not in keeping with the very modest basal FSH levels found in 2 of the other cases. Further studies are obviously needed to establish whether this pronounced rise in FSH after LRH is a consistent feature in girls with early isolated menstruation.

We thank our colleagues for referring their patients for investigation.

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A boy with low-TSH hypothyroidism

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SUMMARY A case of long-standing mild hypothyroidism is described. This was caused by partial TSH deficiency probably of hypothalamic origin, with no other pituitary hormone deficiencies, although with a decreased response of FSH and LH to LHRH.

Low thyroid-stimulating hormone (TSH) hypothyroidism of hypothalamic or pituitary origin is usually accompanied by other pituitary hormone deficiencies (Kaplan, 1975), isolated TSH deficiency in childhood having been described in only one report since the advent of modern TSH assays (Miyai *et al.*, 1971). We report a case of low-TSH hypothyroidism in a child without evidence of other pituitary deficiencies although with decreased response of luteinising hormone (LH) and follicle-stimulating hormone (FSH) to luteinising hormone-releasing hormone (LHRH).

Case report

A 6-year-old boy was admitted with a febrile illness. He was noted to have a deep voice, a protuberant abdomen, and an exaggerated lumbar lordosis. His height was on the 25th centile. He had not developed his first tooth until age 13 months and was said always to have been intolerant of cold. Serum thyroxine (T4) was 42 nmol/l (3·2 μg/100 ml). Our laboratory mean is 110 nmol/l (8·5 μg/100 ml) and range ± 2 SD 75–145 nmol/l (5·8–11·2 mg/100 ml).

Other thyroid function studies included serum triiodothyronine (T3) 2·1 nmol/l (1·37 μg/100 ml), T3 index 109%, free T4 index 39, and TSH<0·6 mU/l. Antithyroid-cytoplasmic antibody (by fluorescent antibody technique) and antithyroglobulin antibody (by tanned red cell test) were negative. A ^{99}technetium scan showed a normally placed thyroid gland. The responses of serum TSH, T4, T3, T3 index, and free T4 index to an IV dose of 200 μg thyrotrophin-releasing hormone (TRH) are shown in the Table. Serum TSH increased to a maximum of 5·2 mU/l at 20 minutes. Bone age was 3·3 years at a chronological age of 6·3 years (Tanner Whitehouse) and skull *x*-ray was normal. *X*-ray of the hips showed advanced changes of Perthes's disease bilaterally. His intelligence was within the normal range although he was having coaching at school for reading and arithmetic.

After 0·25 mg tetracosactrin IM, serum cortisol rose from 343 nmol/l (12·3 μg/100 ml) to 723

Table *Response to an intravenous dose of 200 μg thyrotrophin-releasing hormone*

	Time (min)				*Laboratory*	
	0	*20*	*60*	*180*	*Mean*	*Range ± 2 SD*
TSH (mU/l)	3·5	5·0	2·4	1·7	—	0–5
T4 (nmol/l)	58	69	47	56	110	75–145
T3 (nmol/l)	2·0	2·1	2·1	2·2	1·7	1·0–2·4
T3 uptake %	106	109	104	105	105	97–113
Free T4 index	55	63	45	53	103	70–135

Conversion: SI to traditional units—thyroxine: 1 nmol ≈ 0·077 μg/100 ml, triiodothyronine: 1 nmol/l ≈ 0·65 μg/100 ml.

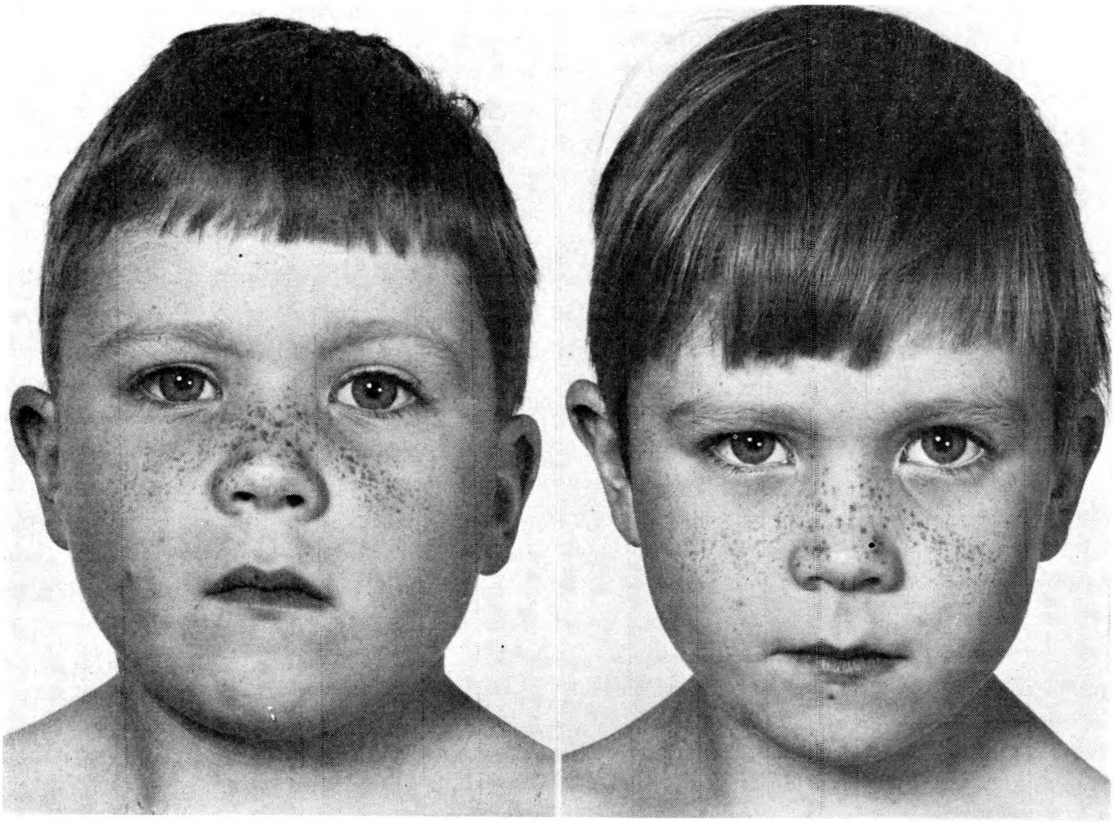

Figure *The patient before and 6 months after treatment with thyroxine.*

nmol/l (26·0 μg/100 ml) at 30 minutes. Basal serum LH was 1·5 U/l and basal FSH 0·9 U/l with no significant rise of either after an IV dose of 100 μg LHRH. Basal serum testosterone was 3120 nmol/l (0·9 ng/ml), basal serum prolactin 260 mU/l, and the maximum serum growth hormone (GH) response in an insulin tolerance test producing adequate hypoglycaemia was 9·6 mU/l, and the maximum serum cortisol 46·7 μg/100 ml (1298 nmol/l). A stimulated GH level of 16 mU/l is regarded by our laboratory as excluding significant deficiency. An exercise test GH level after treatment with thyroxine was 18·7 mU/l, showing that the previous poor stimulation by hypoglycaemia was due to thyroxine deficiency and not to lack of GH. Treatment was begun with oral L-thyroxine increasing to 0·2 mg daily with a resultant rapid change in body habitus and general increase in level of activity (Figure). The height velocity during the first year of treatment was 7·6 cm (equivalent to the 97th centile) and his achievement at school improved considerably with capabilities now described as well above average; special teaching was no longer required. The TRH stimulation test was repeated after one year of treatment (thyroxine being withheld for 8 weeks before the test) as it has been suggested (Boehm *et al.*, 1976) that an improvement in TSH response may occur in isolated TSH deficiency after treatment with thyroxine. Serum TSH rose from a basal level of 2·2 mU/l to a maximum of 4·3 mU/l at 20 minutes, serum prolactin rising from 165 to 750 mU/l. Bone age was 4·4 years at a chronological age of 7·7 years, an advance of 1·1 after 12 months' treatment.

Discussion

We interpret the results in this patient as indicating partial TSH deficiency, possibly of hypothalamic origin, without other clinical evidence of pituitary hormone deficiencies. The response of TSH during the TRH test suggests the presence of some active TSH, while the levels of serum T3 and free T4 index do not suggest either an abnormality of thyroxine protein binding or a defect of peripheral thyroxine metabolism. It is difficult to interpret the significance of the decreased response of LH and FSH to LHRH in a child of this age. The two sisters reported by Miyai *et al.* (1971) were said at the age of 12 and 14 years respectively to have early breast development and detectable urinary LH and FSH. Our patient seems similar to Case 23 of Chaussain *et al.* (1974) who had TSH deficiency with a normal response to TRH but no significant rise of LH and FSH with LHRH.

That this sort of case and other cases of congenital secondary hypothyroidism may be missed, is an objection to the use of TSH rather than T4 as the primary test in screening for neonatal hypothyroidism. However, although this patient has a history of hypothyroidism dating back to neonatal life or at least to early infancy, the hypothyroidism was of mild degree with no deficit in intelligence.

We thank Dr Valerie Marrian for referring this case to the endocrine clinic in Dundee, Miss Margaret Browning and Dr Elizabeth Hunter for endocrine assays, and Dr Constance Forsyth for advice.

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Ring 20 chromosome in a child with seizures, minor anomalies, and retardation

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SUMMARY A patient is reported with seizures, developmental delay, and minor physical anomalies. Karyotype showed a ring formation of chromosome number 20. Previously reported patients with this chromosomal aberration have typically had seizures and behavioural disorders with considerable variation in the degree of physical abnormality and mental retardation. A correct diagnosis in such a case is important for accurate genetic counselling.

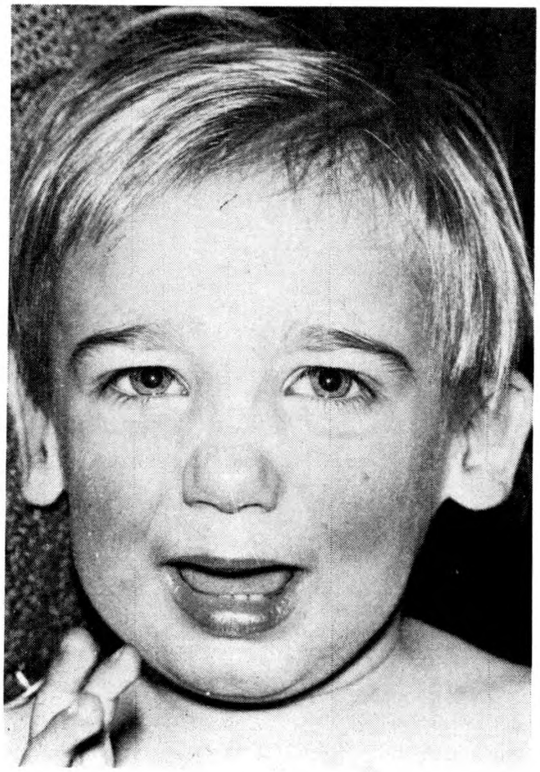
Many new chromosomal syndromes have been reported since the introduction of banding. Most of these are associated with dysmorphic features, multiple anomalies, and mental retardation. A ring formation of chromosome 20, on the other hand, has been reported in patients with negligible physical anomalies, severe seizures, and variable retardation (Table). We report an additional case to emphasise that seizures with slight dysmorphism may be a manifestation of a chromosomal abnormality.

Case report

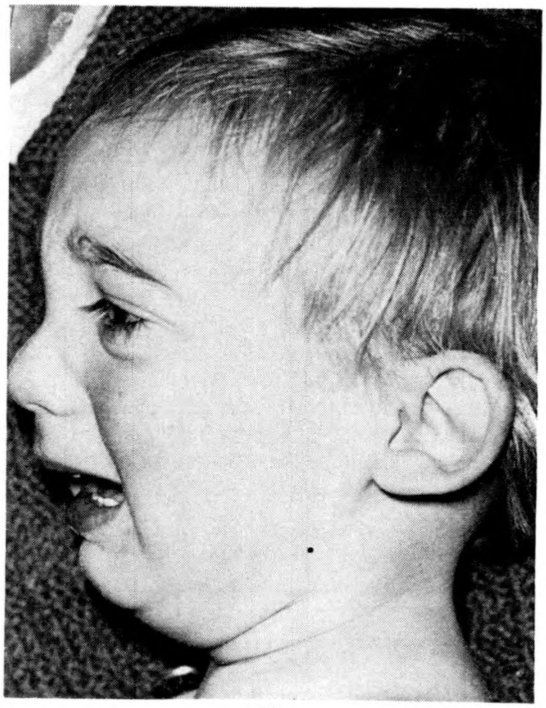
Case 1 was the product of an uncomplicated, term pregnancy and weighed 2800 g at birth. He was a slow feeder initially. He smiled at 7 weeks, sat unsupported at 10 months, crawled at 14 months, and pulled to stand at 20 months. He had no speech at 25 months. At 12 months he was noted to have episodes lasting 30 minutes in which his head turned to the left and his eyes were glazed. By 14 months he was having spells lasting 20 seconds with mouthing movements and twitching of the right arm and leg, followed by excitement. These occurred up to 5 times daily and continued when he was placed on phenobarbitone.

His mother was 36 and his father 39 at the time of his birth. His mother had a nodular goitre. She had had one miscarriage before the patient's birth and has had one subsequently. She has a brother with a cleft lip and palate and an uncle with well-controlled epilepsy. There was no consanguinity.

When examined at 16 months, his weight was at the 10th centile, height at the 25th, and head circumference between the 10th and 25th (46·5 cm) (Fig. 1). Although his face was not strikingly unusual, he did not resemble either parent. He had a sloping forehead, synophrys, long eye lashes, and no epicanthic folds. The nose was small and flattened and he had a long philtrum. The palate was



(*a*)



(*b*)

Fig. 1 *Facial appearance of patient,* (*a*) *full face and* (*b*) *profile.*

moderately high arched and there was micrognathia. The ears were posteriorly rotated and prominent with a poorly developed antihelix. Both testes were descended and he had a glandular hypospadias. He had scattered eczematous patches. There was a groove between the first and second toes, but palmar creases and dermatoglyphics were otherwise unremarkable. Neurological examination was normal except for mild hypotonia.

Routine blood studies including amino-acids, immunoglobulins, and a congenital infection screen were normal. Other normal studies were CAT, electroretinogram, and skull films. An electroencephalogram showed occasional paroxysmal features without clear lateralisation. On the Griffiths's developmental chart he functioned at the 12-month level. A G-banded karyotype showed 3 normal cells and 21 cells with a ring 20 chromosome (46, XY/46, XY20r Fig. 2). Both parents had normal karyotypes. At the parents' request fibroblast cultures were not done.

Discussion

A ring chromosome is formed by the partial deletion of both the long and short arms with rehealing in a ring formation. This is an unusual abnormality and often unstable.

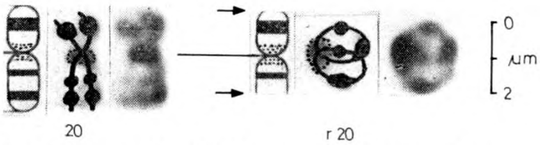


Fig. 2 *Giemsa-banded chromosomes showing, from left to right, drawing and photomicrograph of the normal and the ring chromosome no. 20* (*International Standard Diagram*).

Previous cases. Four other patients with a ring 20 chromosome have been reported (Table). Atkins *et al.* (1972) described a 7-year-old boy (Case 2) with the ring present in most of the cells. Behaviour problems began at one year and grand mal seizures at 6½. His physical examination was said to be normal and IQ was estimated at 50. Faed *et al.* (1972) reported an 11-year-old boy (Case 3) with a ring 20 in 60% of his cells. He too was said to be of normal appearance except for bilateral epicanthi and unusual dermatoglyphics. Temporal lobe seizures started at age 4. They were poorly controlled and associated with behavioural deterioration. His IQ

Table *Patients with a ring 20 chromosome*

Case	*Report*	*Date*	*Age (years)*	*Mental retardation*	*Seizures*	*Behaviour disorder*	*Dysmorphic features*	*Karyotype*	*% of cells with ring 20*
1	Present case	1979	2	+	+	–	±	46,XY20r/46,XY	88
2	Atkins *et al.*	1972	7	+ (50)	+	+	–	46,XY20r/45,XY–20r	94
3	Faed *et al.*	1972	11	± (80)	+	+	±*	46,XY20r/46,XY (3/10 fibroblasts)	60
4	Uchida and Lin	1972	23	+†	+	+	–	46,XX20r/46,XX	22
5	Jacobs *et al.*	1978	27	+ (18)	+	?	–	46,XY20r	100
6	de Grouchy *et al.*	1972	6/12	+	+	–	+	46,XY Fr	100

*Epicanthic folds only, †normal development until grade 6.

was 80. A 23-year-old woman (Case 4) was reported by Uchida and Lin (1972) with a ring 20 in 22% of her lymphocytes, the remaining cells being normal. She was said to have developed normally as a child although she was a 'crib rocker', a head banger, and had nightmares. 'Petit mal' began at age 10 years and grand mal seizures at age 12. Her developmental progress ceased at grade 6 (about 12 years). Her behaviour was erratic, impulsive, and juvenile. She had hyperreflexia and was clumsy in performing finer movements; no dysmorphic features were described. Her IQ was 62. Case 5 was found by Jacobs *et al.* (1978) when screening patients in an institution for the retarded. He had a ring 20 chromosome in all cells counted. He was said to have been normal until 18 months when he had a fall with seizure and fever (41·1°C). At age 27 years, he was profoundly retarded, had mild microcephaly, small testes, kyphoscoliosis, and flexion contractures, but as in the other cases, no dysmorphic features were described.

These patients have several features in common: all had seizures and 3 had behavioural abnormalities of various types (aggressive, immature, impulsive). Intelligence quotients varied from 18 (Case 5) to 80 (Case 3). Our patient also has seizures, developmental retardation, and only minor physical abnormalities. None with a confirmed ring 20 was dysmorphic. However, an infant (Case 6) reported by de Grouchy *et al.* (1972) had a ring formation of an unspecified F chromosome. This child had a dysmorphic face, severely retarded development, and seizures beginning at 3 months. He died at 7 months of age.

When a child presents with seizures, behaviour disturbance, developmental delay, and either no physical anomalies or minor ones, a karyotype may not be requested. Indeed these are common problems and are only rarely associated with a chromosomal abnormality, yet it is important to know when one does exist. The parents of such a child should receive genetic counselling and the recurrence risk will vary with the cause of the problem. The presence of a chromosomal abnormality in the child and normal karyotypes in both parents implies a low recurrence risk with the option of prenatal diagnosis. Mental retardation is variable in this and other chromosomal abnormalities and some of these individuals may reproduce. The recurrence risk in their children is then increased (even when the patient is a mosaic) and amniocentesis is clearly indicated.

The possibility of the chromosomal aberration being secondary to anticonvulsants was raised by Atkins. All the reported patients had seizures and were probably on medication. Acquired deletions of chromosome 20 have been described in various haematological disorders, such as polycythaemia vera (Millard *et al.*, 1968) and acute leukaemia (Kiossoglou *et al.*, 1965). The presence of the abnormality in 3 of 10 fibroblasts examined in Case 3 (Table), its restriction to chromosome 20, and the variety of drugs used make this explanation unlikely.

We thank Dr Edward Brett for allowing us to report his patient and for the many helpful suggestions made by him and by Professor Cedric Carter. We also thank Miss Doreen Farrington and Miss Janette Rae for their help in the cytogenetic laboratory.

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Archives of Disease in Childhood, 1979, **54**, 480–481

Scottish Paediatric Society

At the Annual General Meeting held at the Royal Hospital for Sick Children, Glasgow, on Friday, 17 November 1978, Dr W. H. Galloway was elected President in succession to Dr R. A. Shanks. Dr E. N. Coleman was re-elected Secretary and Treasurer.

The third Jubilee Lecture entitled 'The purpose and philosophy of developmental assessment' was delivered by Professor R. S. Illingworth.

Scientific communications

Follow-up of low birthweight children at early school age. C. M. Drillien. University of Dundee.

88% of an initial sample of 299 infants of birthweights 2000 g and less were followed up to ages 6½–7 years and their progress at school examined. Children who had exhibited transient abnormal neurological signs in the 1st year of life had more problems at school than control children of similar birthweights who had been neurologically normal throughout. Low birthweight children who were considered to have suffered early intrauterine insult were more often excluded from normal school or were more often found to have problems therein than children whose low birthweight (premature delivery or normal dates) was attributed to other causes. Performance in school for survey and control children was correlated with socioeconomic class. For low birthweight children this was a more accurate predictor of later school performance than any other factor.

Radiation characteristics of phototherapy units. I. Smith (introduced), D. H. Wright (introduced), and A. J. Keay. Western General Hospital, Edinburgh.

Clinical studies of the effectiveness of phototherapy in this country seldom include precise measurements of radiation received. A study is in progress to measure the radiant energy output at different wavelengths from various types of phototherapy units using a Macam spectroradiometer. Once these units have been calibrated it is hoped to develop a badge type of radiation measurement (similar to that used in *x*-ray work) for the measurement of light radiation during treatment. The present study gives the measurements of spectral output from various units over both short and long periods, including assessment of the background radiation. First results show that the long-term stability of the units is good but that a considerable difference exists in the spectral characteristics of units from different manufacturers. Background radiation varies to a degree which causes up to a 50% increase in radiation on sunny days. These findings in relation to the clinical effectiveness of the phototherapy units are being studied so that optimal radiation characteristics for treatment by phototherapy can be established.

Faecal viruses and morbidity among babies in Glasgow. T. M. Scott, C. R. Madeley (introduced), B. P. Cosgrove (introduced), and J. P. Stanfield. Stobhill General Hospital, Glasgow.

During a monthly survey of growth and development of babies from birth to 18 months in two Glasgow housing estates, diarrhoea was found to be a common cause of morbidity in babies from the less salubrious area. Identification of faecal viruses in stool samples taken from these infants led to a more extensive survey. Weekly visits were paid to 27 infants in their homes so that details of illnesses could be recorded and stool samples collected for EM. Faecal virus excretion during hospital admissions was monitored by daily sampling if possible. The findings show that although virus excretion is common and is frequently recurrent, symptoms of illness are not inevitable. The pattern of excretion during hospital admissions is complicated by the multiplicity of virus types seen during a single admission, and the occurrence of hospital-acquired infection. Identification of enteropathogenic *Escherichia coli* and viruses in combination raises doubts about the validity of ascribing symptoms to any single agent.

Genetic component in febrile seizures. J. B. P. Stephenson. Royal Hospital for Sick Children, Glasgow.

It is generally recognised that there is a genetic basis to many febrile convulsions (FC). The usual explanation is that the convulsive threshold is lower in early childhood; by this it is meant that the *epileptic* convulsive threshold is lower. 630 children referred for EEGs after at least one FC and who also had ocular compression were studied, and the resulting cardiac asystole was measured. Prolonged cardiac asystole after this manoeuvre was found to be directly related to a family history of FC. Experimental 'anoxic seizures' after excessive oculocardiac reflex were also studied in approximately 100 children in whom it was found that the convulsive threshold—the *nonepileptic* convulsive threshold—was related to age, and was low at ages when genetic FC are common. The genetic basis for familial FC is an excessive sensitivity of the vagocardiac reflex at an age when the anoxic/ischaemic convulsive threshold is low. The details of this mechanism and its relation to cerebral pathology and to epilepsy, have yet to be elucidated.

Change of reference style

From January 1980, the *Archives* will change its style for citing references and will follow the number system. We are making this change in order to conform with the 'Vancouver style' of uniform requirements for manuscripts submitted to biomedical journals.

Previously the *Archives* has used the Harvard reference system. Its advantages and disadvantages compared with those of the number system have seemed evenly balanced, but the editors have been aware of the burden imposed on authors and their secretaries by the different styles which different journals require. Therefore, with the unanimous agreement of the editorial committee, we have decided to support a move whereby a large—and increasing—number of major medical journals will accept manuscripts presented in one agreed style.

The system numbers references consecutively in the order in which they are first mentioned in the text. References are identified in the text by arabic numerals. For further details see instructions to authors inside the front cover, and the references cited.[1,2]

From now onward all manuscripts submitted should accord with the new style.

[1] International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979; **1**; 533–535.

[2] Lancet. The Vancouver style. Uniform requirements for manuscripts submitted to biomedical journals. *Lancet* 1979; **1**; 429–430.

Archives of Disease in Childhood, 1979, **54**, 482–486

Correspondence

Conservative care of the newborn baby

Sir,

We were disturbed to read Dr Hughes-Davies's report (*Archives*, 1979, **54**, 59) and should like to explain why we regard some of his conclusions as unjustified.

Dr Hughes-Davies describes his hospital care of 14 892 newborn infants delivered in Salisbury during 1969–76. In his management of small or ill babies he places emphasis on correct posture and temperature, early feeding, and minimum handling. With this and with his isolation policy we are in complete agreement. However, we then part company. Modern methods of neonatal monitoring are not used in Salisbury. Nothing is given intravenously. Ventilation and positive pressure devices are not used, nor is phototherapy. Apnoeic attacks are treated with funnel air and oxygen (presumably without monitoring the infant's blood oxygen tension).

Dr Hughes-Davies justifies his practice by claiming that neonatal complications were 'seldom met' and that his babies 'did well' at follow-up. The only data he presents concern first-week neonatal mortality. Then, on the basis of a number of unsatisfactory comparisons, he concludes that his results compare favourably with those achieved by 'more intensive and active intervention'. Furthermore he extols the economic benefits of his approach which requires less equipment, fewer staff, and allows nurses and doctors to get more rest! As one of us has just completed a study of paediatric staffing and equipment for newborn care on behalf of the BPA, we are conscious of the deplorable deficiencies that exist up and down this country. Unless countered, Dr Hughes-Davies's views may well seriously impede efforts currently being made to correct this sad state of affairs. It is this that prompts us to write and to compare the Salisbury figures with our own. Before doing so, we should like to discuss the various comparisons made by Dr Hughes-Davies. Firstly, he compared his results with those reported for England and Wales, the unjustified implication being that 'intensive care' is practised everywhere except in Salisbury. However, the national survey of newborn care referred to earlier shows conclusively that only a handful of the 252 special care baby units in this country have the necessary experienced resident staff and equipment to provide more than a token intensive care service, if that. Incidentally, in making his comparison of first-*week* mortality Dr Hughes-Davies failed to indicate in the caption to his Table 2 that the figures for England and Wales referred to the whole of the first *month* of life, not the first week. Similar criticisms apply to his comparison with 'Wessex neighbours' about whom no information is provided. Comparison is made between the mortality of very low birthweight infants in Salisbury, where presumably most if not all of such infants are *inborn*, and University College Hospital where, in contrast, the majority are *referred* from a wide metropolitan area. We would submit that no conclusion may be drawn from such a comparison.

We should like to compare the Salisbury figures with our own from Southmead Hospital. It should first be explained that although our intensive care service has been steadily improving since it was initiated in 1970–71 (Figure) and although we are now better provided for than most, we still have significant shortages in both staffing and equipment. The special care baby unit of 36 cots at Southmead serves the 4800 inborn infants and acts as a regional referral centre. Therefore many more problem cases may be expected than in Salisbury. Two statistics demonstrate this: the incidence of low birthweight and fatal congenital malformation were respectively 68 and 50% higher at Southmead in 1973 than the average for Salisbury, 1969–76. Thus, with similar quality of care the early neonatal mortality rate (NMR) for Southmead might be anticipated to be about 50% greater than that for Salisbury. In fact the reverse was the case. The NMR for Salisbury for the whole period 1969–76 was 9·3/1000, while that for our department in 1973 was 5·5/1000. The figures for low birthweight infants were 109/1000 for Salisbury and 36/1000 for Southmead; for infants in the birthweight group 1501–2000 g they were 167/1000 for Salisbury and 38/1000 for Southmead, while in that for the group 2001–2500 g they were 19·9 and 8·0/1000 respectively. Incidentally, it seemed reasonable to pool the Salisbury figures in view of the small annual numbers and the fact that 'the care of the babies was unchanged' during the whole period.

A fairer and even more striking comparison in favour of intensive care may be made if infants weighing <1000 g at birth and infants with fatal congenital anomalies are excluded from the analysis. If this is done then the remaining 'preventable' NMR for Salisbury was 5·8/1000 livebirths while that for Southmead in 1973 was 3·0/1000; by 1978 the Southmead figure had fallen to 1·7/1000. A final comparison needs to be made for babies of very low birthweights (500–1500 g). The NMR for 105 such infants in Salisbury was 505/1000 while that for the 49 similar infants at Southmead in 1978 was 224 or, if fatal malformations are excluded, 174/1000 (a survival rate of 83%).

If we assume that, on average, 600 000 infants are born in England and Wales each year, then it can be calculated that a country-wide application of the neonatal care advocated by Dr Hughes-Davies would lead to 2460 more 'preventable' early neonatal deaths each year among normally formed liveborn infants over 1 kg than would be the case if the 1978 Southmead standard were adopted instead. Nor does this figure take into account the fact that the Southmead figures were loaded with referred problem cases. In addition, as the late Professor W. C. M. Nixon wrote in 1963: 'Like an

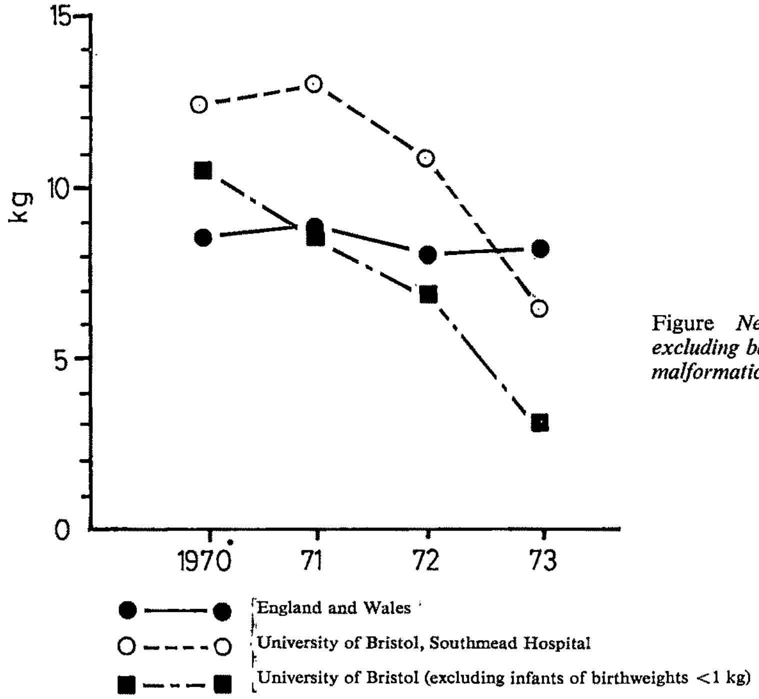

Figure *Neonatal mortality rates 1970–73, excluding babies with fatal congenital malformations.*

iceberg, we see only a proportion of the ill results, the deaths. But we must not forget the submerged and larger fraction, the near deaths and the harm which they cause'—*the long-term handicaps*. As to the cost–benefit of prevention, our admittedly amateur calculations suggest that the provision of good newborn care is likely to pay for itself at the very least 20 times over and perhaps 100 times or more.

In conclusion, we should like to make the following points: (1) We warmly support Dr Hughes-Davies's emphasis on the importance of the fundamental principles of keeping small sick infants warm and fed, of nursing them prone, and of handling them as little as possible. (2) We deplore and reject his denial of the benefits of modern intensive monitoring and therapy for infants that require such support. (3) We have some sympathy with his view that a great deal of intensive care *as currently practised* with inadequate staff and facilities may be counterproductive—although we have even more sympathy with the nurses and doctors who struggle on in spite of the difficulties. (4) Finally, we would agree with Dr Hughes-Davies when he stresses the critical importance of good antenatal and intrapartum care in reducing perinatal mortality.

P. M. DUNN AND B. D. SPEIDEL
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Dr Hughes-Davies comments:

The letter from Dr Dunn and Dr Speidel raises some interesting points.

The comparison of very small babies was, as stated, with those born in University College Hospital. I excluded those transferred because we do not know from what population they came. Paradoxically the figures suggest that the transferred babies did at least twice as well as those born on the spot, presumably because the tiny and the weak died before they could be moved; and it may be that this effect favours Southmead too. London has many more immigrants than Salisbury, and some of these babies are likely to be more mature for a given weight than ours; hence the breakdown by gestation in Table 4. I still think the comparison is valid enough to make the point that we have far to go in helping babies of <1000 g.

The Wessex neighbours were Basingstoke, Bournemouth, Dorchester, Portsmouth, Southampton, and Winchester. The first-week figures were not collected by me, but I was allowed to use the totals. Salisbury compared favourably with the others individually, and I am not sure why the comparison is rejected.

I had available only the 4-week national figures sufficiently broken down by weight, and I expected that the table would be read in conjunction with the text. If our monthly figures had been included there would have been little difference, although some babies may well have died at home or elsewhere without our knowledge. Those of <2500 g who died in the 2nd–4th weeks were: a 2400 g mongol with Dandy-Walker syndrome (at 4 weeks), a 2400 g baby with congenital viral pneumonia (in the 2nd week), a cot death of a 1420 g baby at home (in the 3rd week), and a quadruplet weighing 900 g who died from *Klebsiella* pneumonia (at 3 weeks).

Despite Dr Dunn and Dr Speidel's warning, the Southmead figures fail to distinguish between babies born there and elsewhere (or so I infer from the mention of problems from afar which is otherwise irrelevant). I agree with their submission that this invalidates further comparison, but I shall continue. The category 500–1500 g contains a mixture of babies, some with an excellent chance of survival and others with none, and without further breakdown it is meaningless. If their distribution matches that of Salisbury in 1974–76, there can have been no undeformed death > 750 g in 1978. Is this so? Or do they have more babies of 1400 g and fewer of 500 g because of transfer from outside? The advantage of selection to the receiving hospital is, of course, offset by a worsening of the figures in the referring hospital, unless both claim the baby in which case the regional figures will show a spurious improvement. A similar error of selection is produced by counting babies at the nursery door instead of at birth.

Even if figures are properly derived and presented raw by number, year, weight, and origin, they provide no basis for comparison unless the state of the babies coming into care is the same. This depends on the pattern of motherhood which perhaps changes uniformly throughout a wide region, and of obstetric care which shows much local variation and can change abruptly as doctors move and methods (whether alcohol drips or caesarean delay times) alter. Both Salisbury and Bristol show a similar decline in mortality over the years—the Salisbury figures corresponding to the lower University of Bristol line of the Southmead chart are 5·6, 8·9, 9·5, 7·4, 3·7, 4·2, 2·7, and 2·2 respectively for the years 1969–76. In Bristol the trend may be due to the institution of intensive care in 1970; but in Salisbury, where paediatric care has been held constant, the steady improvement over the years must be due to better mothers or to better care before birth. Incidentally this makes the pooling of figures over the years unreasonable. Even in 1976 it is likely that Salisbury which lacks senior registrars, had no convenient theatre or nearby outpatient clinics, and has insufficient fetal monitors, was handicapped compared with Bristol; but if comparison is to be made, it should be with the later years. I have already dealt with the likely bias among Southmead's lighter babies; for those from 2000–2500 g where transfers are less likely, our figures match (Southmead 8·0, Salisbury 9·5 per thousand for 1974–76, a statistically insignificant difference of about one baby in 7 years).

Perhaps a better approach is to look at the individual babies and ask why they died. This I attempted to do for babies over 1000 g in Table 3 by excluding those we could not or would not wish to save by reason of lethal uncorrectable deformity, tentorial tear proved at necropsy, or severe intrapartum asphyxia suggested by prolonged apnoea at birth. Again looking at 1974–76, there were 5 such deaths, one after operation elsewhere, and 2 in babies delivered far away without help and admitted moribund. This gives a paediatrically preventable NMR of 0·9/1000 which is not of course fairly comparable with Southmead's preventable NMR of 1·7 in 1978.

An administrator doomed to view the world through marks on paper, might estimate from the Southmead graph that, spread over the country, their methods would have killed 5000 babies in 1970–73. Having a profound distrust of vicarious statistics, and recognising Bristol's long record of distinction in the care of children, I know that this would be nonsense, as are most such computations. So much for the numbers game, by which we need set no great store.

Like modern rock climbing, intensive care has developed awesome techniques, which although sometimes of use to the scrambler, threaten to become an end in themselves, so that the best way to take a baby up Eiger appears to be by the north face. It is no longer entirely facetious to suggest that a patient with a heart attack sometimes needs intensive care to survive the effects of intensive care, and that those who succumb to this may more or less balance those who would have died if they had stayed quietly at home under skilled supervision after initial resuscitation. Whether this is true of newborn babies I do not know. Neither do Dr Dunn and Dr Speidel, but I hope they will take the opportunity to find out by subjecting some of their babies to the Salisbury usage (having first read my paper a second time to correct their inadequate summary of the method). In the meantime we should remember that truth does not come out of the mouth of a committee, and that the safest response to uncertainty is diversity. As Dr Dunn and Dr Speidel so kindly say, we have a lot in common, and of course research must continue, although perhaps it should not be mimicked too soon or too widely. But all nurseries really should divulge their results in proper form, if necessary in confidence, perhaps to Sir Cyril Clarke and Professor Neville Butler to whom our babies owe so much. And perhaps too they should end their day with a Litany—'From gastric oxygen, streptomycin, delayed feeding, and arterial thrombosis, Good Lord Deliver Us'—it will be a long one, and there is no reason to think it is not lengthening. I may even join it myself.

T. H. Hughes-Davies
Central Hospital,
Honiara,
Solomon Islands

Sir,

I should like to make some comments on the paper by Hughes-Davies (*Archives*, 1979, **54**, 59). I think there are several points that need to be made, in view of his allegations that neonatal intensive care is of little benefit.

Firstly, his figures are not as good as he would like to make them. For infants of birthweights 1001–1500 g, apart from one very good year in 1976 which all units get periodically, his figures are considerably worse than those quoted currently from neonatal intensive care units in the UK. Furthermore his figures for 1500–2000 g report a neonatal mortality which is again two to three times higher than that reported from such units. To compare with his Wessex neighbours is unjustifiable—clearly they also need better intensive care facilities, and to compare with England and Wales for the first *month* is again quite unsatisfactory. In addition there is much evidence to show that the overall standard of perinatal and neonatal care in this country is a disgrace.

Secondly, I find his Table 3 unsatisfactory. Prematurity is not a diagnosis I recognise between 1001 and 1500 g. I suspect all those 7 babies died from hyaline membrane disease (HMD)—untreated. Furthermore, column one in Table 3 only contains 12 babies, whereas 26 babies of this birthweight died. Some may have had lethal deformities, but presumably the majority died of intrapartum asphyxia. We have shown (Roberton and Tizard, 1975) that it is such small babies who suffer intrapartum asphyxia that suffer the most severe HMD, but many of these are salvagable in a neurologically intact state by modern techniques in neonatal intensive care.

Thirdly, I would hope that all paediatricians would now regard it as a completely unsatisfactory standard of care to provide face mask oxygen for very low birthweight babies without control of arterial oxygen tension.

One very important factor to consider when such data are provided is what are the obstetricians in his unit doing with women with major complications of pregnancy and seriously compromised fetuses at gestations of 28 to 30 weeks? Do they feel they have no alternative but to try to keep the pregnancy going for another week or two with subsequent intrauterine death, or do they in fact send such women to be delivered in a perinatal unit providing modern standards of intensive care? Many of us who run neonatal intensive care units know the latter practice is increasingly common where the local standards of neonatal care are inadequate.

Neonatal intensive care does save lives. The Table shows that neonatal mortality in Oxford was reduced by half over a 3-year period during which an adequate programme of intermittent positive pressure ventilation (IPPV) was instituted. The standards of care described by Dr Hughes-Davies may have been satisfactory in Salisbury, they may be satisfactory in the Solomon Islands, but I hope that all readers of the *Archives* will reject them as being unsuitable for the UK in 1979.

Table *Numbers of neonatal deaths, and infants surviving IPPV over 3-year period*

Year	*Neonatal deaths*	*Infants surviving IPPV*
1971	41	1
1972	28	9
1973	21	21

Reference

Roberton, N. R. C., and Tizard, J. P. M. (1975). Prognosis for infants with idiopathic respiratory distress syndrome. *British Medical Journal*, 3, 271–274.

N. R. C. Roberton
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Dr Hughes-Davies comments:

Some of the points made by Dr Roberton are covered in my reply to Dr Dunn. I agree that prematurity is an unsatisfactory diagnosis at any weight. Five of our 1001–1500 g babies so labelled were born in 1970 when I was in Saigon and I have no other details except that 3 were 28 weeks or less, and 2 were second twins; it is likely that babies were disturbed more then than in other years. Of the other 2, one, born in 1974, weighed 1020 g supposedly at 25 weeks and died at 4 hours after repeated apnoea; the other died at 24 hours in 1971 and weighed 1420 g; histology showed only atelectasis, and neither had HMD. Of the 26 babies dying in this weight range, 9 had prolonged apnoea at birth, 6 in 1971 or before, one in 1972, and 2 in 1974. They did not have HMD. One of the most striking features was the mildness of respiratory distress in babies handled gently in Salisbury (and in the Solomon Islands where I was pleased to meet a very fit baby now 14 months old who weighed 750 g at birth and who was cared for conservatively by Dr Ogatuti). Perhaps babies prefer pastures to battlefields—certainly their need for high concentrations of oxygen is rare, and its risks may be balanced by those of an indwelling arterial catheter which I am sure Dr Roberton would agree is the only worthwhile method of monitoring yet available. Even this is vitiated by a 10% leak from the ductus arteriosus.

No baby to my knowledge was transferred elsewhere either before or after birth except for surgery, and the distribution of weights matches the country as a whole. Patterns of intervention varied as they did elsewhere over the period, but our relations with the obstetricians were good, and I do not think our practices influenced theirs.

Of course intensive care saves lives; and of course it demands a price which can perhaps be justified in hospitals lucky enough to enjoy the skills of Dr Roberton. But I hope he will read my paper again. I have erred if he reads it as an attack on intensive care. It was simply an account of my reaction to practices current 13 years ago, which he suggests are still common today; and I hope he will regard the results as a control group for his own if he cannot bring himself to try the method. Dr Roberton's Table shows a fall in neonatal deaths about the same proportionately as occurred in Southmead and Salisbury and probably elsewhere in the first half of this decade; and, in the absence of an adequate library, I cannot comment on the number surviving IPPV which must depend on the number submitted to it. Again I would ask first for reliable figures; and second for a demonstration, perhaps in a single region, that Dr Roberton's methods can be as effective in less fortunate hands.

T. H. Hughes-Davies
Central Hospital,
Honiara, Solomon Islands

Hypopituitary dwarfism and breech delivery

Sir,

Recent investigations by Rona and Tanner (*Archives*, 1977, **52,** 197) show that breech delivery is a common occurrence in patients with idiopathic hypopituitary dwarfism.

We conducted a survey on the type of delivery in 118 patients with idiopathic growth hormone deficiencies (age range 4–18 years) and in 121 healthy control children.

Among the cases of hypopituitary dwarfism, 43 had isolated and 'total' growth hormone deficiency, 64 had isolated and 'partial' growth hormone deficiency (Priece and Tanner, 1976; Boscherini *et al.*, 1978), and 11 had multiple pituitary trophic hormone deficiencies.

The incidence of breech delivery was much higher in patients with hypopituitary dwarfism (19·6%), than in the control group (1·6%) (Fisher's exact probability test: $P<0\cdot01$). Moreover we observed that breech deliveries were slightly more common in patients with isolated and 'partial' growth hormone deficiencies, certainly more common in patients with isolated and 'total' growth hormone deficiencies, and were very common in patients with multiple pituitary trophic hormone deficiencies (Figure). The trend was significant when analysed by Armitage's χ^2 test ($P<0\cdot01$).

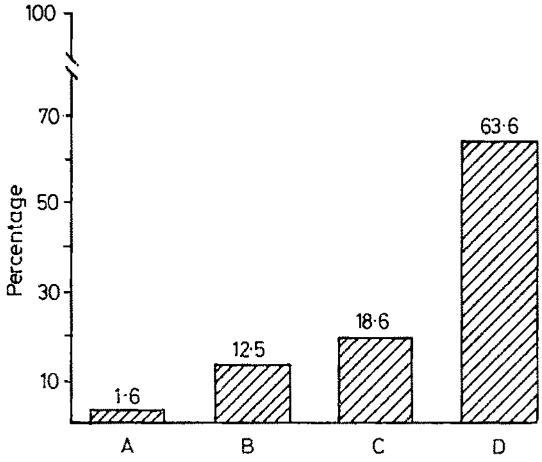

Figure *Incidence of breech delivery in patients with hypopituitary dwarfism. (A) Control group, (B) partial growth hormone deficiency, (C) total growth hormone deficiency, (D) multiple pituitary trophic hormone deficiency.*

The high frequency of breech delivery in our patients and the close relationship between the frequency of podalic presentation and the severity of functional pituitary impairment support the view that breech delivery plays an important pathogenetic role in idiopathic hypopituitary dwarfism.

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Paediatric Ophthalmology Study Group

Sir,

This interdisciplinary study group on Paediatric Ophthalmology was founded by the late Dr Ronnie Mac Keith. It includes ophthalmologists, paediatricians, neurologists, psychologists, teachers, social workers, and others involved in the care of visually handicapped children. Its objectives are to further the knowledge of the subject, exchange ideas, and stimulate interest in this field to the eventual benefit of children who are visually handicapped. The group meets twice a year; in the autumn at the Newcomen Centre, Guy's Hospital, when formal papers followed by discussion are presented, and early in the year when visits are made to research units, special schools, or to any department concerned with the problems of paediatric ophthalmology. The present Convener is Dr Neil Gordon, Booth Hall Children's Hospital, and the organisation of the group is supported by the Spastics Society.

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Archives of Disease in Childhood, 1979, **54**, 487–488

Book reviews

Atherosclerosis: Its Pediatric Aspects. Clinical Cardiology Monographs. Edited by W. B. Strong. (Pp. 330; illustrated + tables. £12.85 hardback.) Grune and Stratton: New York. 1978.

This monograph comprises a series of papers about the risk factors for atherosclerosis. This is a popular subject at the present time and it certainly is useful to have an up-to-date statement of the art. I do not think that the book contains anything very startling or new, but it is a good starting point for anybody who wishes to get into the field.

There is first a generally rather optimistic overview, which is summed up in the Foreword, where the first sentence concludes: '. . . the best available data suggest that if 11 known risk factors were controlled in adults, *only* 50% of the cases might be prevented' (my italics).

One of the most intriguing facets of atherosclerosis concerns its geographical pathology and the chapters from Newman and Strong and from Hames and colleagues in Georgia concentrate on this. Henry Neufeld contributes some more of his intriguing arterial pictures, which have much to do with the genetic and environmental determinants of atherosclerosis. Lipids, lipoproteins, hypertension, smoking, nutrition, and exercise are considered in some detail.

I found the most interesting chapter to be the one about atherosclerosis prevention in Arizona. Nobody knows whether such programmes will actually reduce the incidence of it, but as Henry McGill is reported to have said: 'Nobody has ever shown that high cholesterol levels, high blood pressure, or smoking is good for your health, nor has anyone demonstrated the benefits of obesity or sedentary living habits'.

I am glad to have this book and I hope that it will be available in the larger libraries. I think academic departments of paediatrics ought to possess it, but I would not advise every paediatrician to go out and buy his own copy.

C. G. D. BROOK.

Atlas of Abdominal Ultrasonography in Children. By G. F. Gates. (Pp. 283; illustrated. £16.50 hardback.) Churchill Livingstone: Edinburgh. 1978.

Although this book is entitled *Atlas of Abdominal Ultrasonography in Children*, it is much more than that. It is a summary of differential diagnosis and of the most appropriate and rewarding investigations that should be performed in abdominal disorders, with the emphasis on radioisotope and ultrasonic scanning.

The author is Associate Clinical Professor of Radiology and Director of the Department of Nuclear Medicine and Ultrasound in the Children's Hospital in Los Angeles, so it is easy to see why he has approached the subject of ultrasonography from this, the ideal point of view.

There are chapters on the liver and spleen, biliary system (including the pancreas), midabdomen, pelvis, and kidneys. The introduction gives the essential points that should be looked for by the referring clinician on the indications for ultrasonic scanning and the limitations of it, and there is useful and practical advice for those starting an ultrasonic scanning programme. The complementary nature of ultrasonic scanning to diagnostic radiology and radioisotope imaging is emphasised, and its noninvasive nature stressed, explaining its ready acceptance by most children. Much of the book is devoted to illustrations which are mainly of good quality, although the text is interesting and readable.

At £16.50 the book is a good buy for departments of diagnostic imaging. It can be recommended to all those who scan paediatric patients, to the referring clinicians, and those who are about to sit an examination in diagnostic imaging or who wish to bring themselves up to date with recent advances in this field.

BARBARA C. KING

Nutrition, Immunity, and Infection. Mechanisms of Interactions. By R. K. Chandra and P. M. Newberne. (Pp. 246; illustrated + tables. $22.50 hardback.) Plenum: New York. 1977.

The authors have addressed themselves to one aspect of clinical immunology that is currently exciting interest and consuming a good deal of effort in research and clinical immunology. They draw attention to the fact that perhaps a hundred million children suffer from kwashiorkor and that minor forms of nutritional deficiency must therefore be very much more common. It has been widely believed that malnutrition is associated with an increased hazard of infection, and so a scientific text examining this possibility more fully must be widely welcomed. Their book, which fills 233 pages including bibliography, is divided into 9 chapters. At the beginning a careful, detailed, and up-to-date account is given of the immunological resources of the developing human organism. There follows a full and helpful chapter concerned with the assessment of nutritional status including nutritional aspects of fetal life. The middle section of the book deals with the interactions between infection and immune responses, and the metabolic effects of infections. This section is detailed and is linked, as other sections are, to a full and up-to-date bibliography. Towards the end there is a section dealing with those topics in a comparative manner referring to research in nonhuman species, and finally, there are useful sections on the wider biological implications of infection, nutrition, and immunity, together with a comment on further research needs.

The book is well illustrated and contains a number of useful factual tables. It would perhaps have been helpful to have a numbered list of headings with the title of each chapter since each paragraph is carefully numbered. With this minor criticism the book can nevertheless be strongly recommended to clinical researchers and those who are interested in related subjects of immunology and nutrition. The book provides a very good framework and is not too expensive for purchase or too lengthy to read. It is to be hoped that the authors will be prepared to maintain the book through a number of editions for although it is now fully up to date one can imagine that in this expanding subject revision will be necessary within 3 or 4 years. This shows the value of the book rather than affords a criticism.

C. B. S. WOOD

Paediatric Cardiology. By R. H. Anderson and E. A. Shinebourne. (Pp. 616; illustrated + tables. £18.00 hardback.) Churchill Livingstone: Edinburgh. 1978.

This book is an account of the proceedings of the Second European Symposium sponsored by the British Heart Foundation and organised by the editors. The purpose of the symposium was to concentrate on some of the more important growing aspects of the diagnosis and management of congenital heart disease, and contributors from America and Europe were chosen for their special experience in the subjects covered. These of necessity tend to be rather restricted, so that the book in no way represents a comprehensive account of modern paediatric cardiological practice as its title might suggest.

As with all international symposia, the standard of contributions is variable. There is an excellent account of the new terminology in congenital heart disease and its relevance to the precise diagnosis of complex lesions, using the method of sequential chamber localisation which the editors themselves have done so much to promote during the last few years. Likewise, the sections on ventricular septal defect, Fallot's tetralogy, and atrioventricular canal defects, contain interesting material which is well presented. In particular, Rudolph's introductory review of ventricular septal defect in infancy is a small masterpiece of clarity and concise organisation of essential information. However, in other parts of the book, especially where the subject matter is more abstruse, both text and format tend to suffer from an unfortunate degree of repetitiveness. The free discussion that follows each major section, and which is generally of a high standard, enhances the interest and understanding of each subject.

Because of its specialised and selective content, this book cannot be recommended as a work of reference for undergraduates or noncardiological postgraduates. Nor will it be of value to general paediatricians. However, for those engaged in the challenging and fascinating task of diagnosing and treating infants with complex congenital cardiac defects it will provide a fund of valuable and up-to-date information.

T. A. H. ENGLISH

Reflux and Renal Scarring. British Journal of Radiology Supplement 14. By P. G. Ransley and R. A. Risdon. (Pp. 35; illustrated + tables. £3.60 (£3 to members of British Institute of Radiology) paperback.) British Institute of Radiology: London. 1978.

It might seem a difficult task to review an experimental study the results of which so closely accord with the reviewer's own clinical experience and views. Nevertheless it can be said without reservation that this supplement deserves the close attention of all those who are concerned with the clinical care of children with urinary infection or vesico-ureteric reflux (VUR), and with the prevention of renal scarring and its possible consequences.

The association of VUR, renal scarring, and urinary infection has been recognised for some time, but the mechanisms have been less clear and there remain a number of unexplained clinical anomalies—such as the child with VUR who has recurrent urinary infection but persistently normal kidneys. Hodson's pioneering experimental studies had confirmed that when VUR was induced in pigs, the development of renal scarring was confined to those areas of the kidney where intrarenal reflux (IRR) had been visualised. In this book Ransley and Risdon set out to investigate the relative importance of urodynamic factors, infection, and the morphology of the renal papillae in the development of such scars. The result was a carefully planned and controlled series of experiments presented clearly and readably and assisted with admirable diagrammatic, radiological, and histopathological illustration. The reasons for the choice of the experimental animal (piglet), and the precise techniques used, are also discussed succinctly.

The basic findings are summarised as follows: 'Segmental chronic pyelonephritic scarring in the young pig depends upon vesico-ureteric reflux of infected urine. Individual scars are formed at the sites of intrarenal reflux and this in turn is determined by the form of the renal papilla, some allowing intrarenal reflux and some preventing it.'

The morphology of the pig's kidney resembles that of the human in many respects and there is a close similarity between the induced and the naturally occurring renal scar. If the analogy between the experimental and clinical situation is to be pursued, then the implications of this study must include a reappraisal of the need for ureteric reimplantation and its timing, and an emphasis on the importance of urinary infection, its early diagnosis, and adequate treatment.

Paediatricians, urologists, radiologists, and pathologists, will all enjoy reading this book. So too will those who are excited by observing the emergence of convincing answers from a carefully planned study.

JEAN M. SMELLIE

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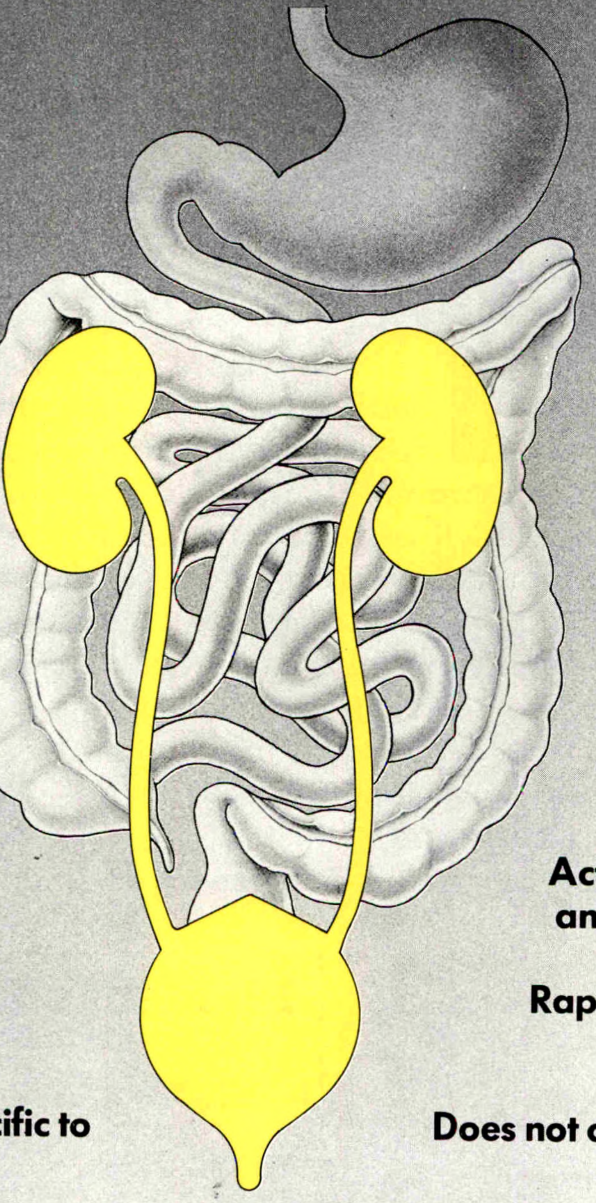

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Archives of Disease in Childhood, 1979, **54,** 489–491

James Spence Medallist, 1979

Kenneth William Cross

Kenneth Cross was educated at St Paul's School, London from 1930 to 1935 and then at St Mary's Hospital (London University) where he had won a Moran Scholarship.

After house appointments early in the war he served in the emergency medical service and was graded as a physician. He was in the Friends Ambulance Unit in China immediately after the war and returned to St Mary's in the physiology department under A. St. G. Huggett. At this time (1948) he started work on the ventilation of the newborn infant and was one of the first to apply objective physiological techniques to the clinical problem of resuscitating the newborn baby. He continued in the field of neonatal research thereafter.

In 1958–59 he was a visiting professor in the Cardiovascular Research Institute at San Francisco, directed by Dr Julius H. Comroe Jr, where he initiated neonatal research with a trio of young paediatricians, Marshall Klaus, William Tooley, and the late Kurt Weisser of Basle. From this small beginning grew what became one of the largest paediatric research groups in the USA.

In 1960 he became professor of physiology at The London Hospital Medical College, and in 1963 obtained a Medical Research Council Group to study respiration and metabolism in the newborn. Many of his publications have appeared in the *Journal of Physiology*, while in 1973 he organised for the Physiological Society the Joseph Barcroft Centenary meeting, and edited the account of that notable international symposium.

In presenting the James Spence medal to Professor Cross at the annual general meeting of the British Paediatric Association at York on 28 March 1979, the President, Professor O. H. Wolff spoke the following citation:

'Kenneth Cross is this year's James Spence Medallist. Our Association recognises the great contributions made to the advancement of paediatric knowledge by workers in allied disciplines. The Spence Medal has now been awarded on 18 occasions and among the medallists there are immunologists, geneticists, biochemists, physiologists, psychiatrists, in addition to paediatricians. But, I am afraid, we have not always been generous in openly acknowledging how much we paediatricians owe to our colleagues in the basic sciences. Without them the scientific basis of paediatrics would indeed be shaky. It is today my sad duty to have to remind you that when Kenneth Cross's name was first put forward for membership of the Association, the proposal was unsuccessful because, it was said, paediatricians saw no reason to include a physiologist among their members. By 1957 Kenneth's contributions to the physiology of the newborn were so many, so fundamental, and of such immediate relevance to paediatric practice, that at last he was elected a member. It is good that today we can make amends for our earlier lack of vision and give Kenneth the highest award of our Association. Kenneth has not had an easy professional life; paediatricians were slow to recognise the importance of his work for paediatrics, and physiologists found it impossible to believe that fundamental work could be done on the human newborn. At the same time as the first proposal for membership of the BPA was turned down, Kenneth

was told by his professor at St Mary's that it was time he stopped playing about with babies and got down to some proper physiology.

'Fortunately Kenneth is tough and these rebuffs further inspired him and stimulated his scientific curiosity and inventiveness, and his papers on neonatal respiratory physiology, written with clarity and economy of words, continued to be a stimulus to all of us. Even physiologists have over the years recognised the great merit of Kenneth's work and I believe that he may even have succeeded in persuading them that the human neonate, despite all his imperfections, is not to be despised as an experimental subject. The neonatal rat, guinea-pig, rabbit, pig, and lamb are no longer the only heroes on the stage of perinatal physiology. Accordingly, last year, Kenneth was invited to give the annual review lecture of the Physiological Society.

'Kenneth is tough, not only in spirit, but also physically. A Rugby football player of exceptional skill, he was admitted to St Mary's Medical School on a Rugby Scholarship. He drives an open car in all weathers and cannot understand why, during the arctic conditions of this winter, and despite rail strikes, some of his friends were a little reluctant to accept his offers of a lift.

'As head of his academic department, Kenneth is known for his personal concern for the problems of all members in his department and for his complete fairness. He can be firm when the occasion demands but he is no disciplinarian. In particular, he objects to being called 'Sir' by the more attractive girl students. I cannot tell you how he likes best to be addressed by them. He is respected and revered by his department, but unlike many academics who are prepared to give of their all for the benefit of their *own* department but show little concern for the welfare of the whole medical school or university, Kenneth has a wider sense of responsibility. It is, therefore, not surprising that his colleagues elected him Chairman of the Academic Board, and that among many other commitments he serves the British Council on its Medical Advisory Committee. Committees benefit greatly from his wisdom, delightful dry sense of humour, capacity for constructive criticism, and his willingness to make the needed unpopular remark.

'As a teacher, he has given much to paediatricians, many of whom have had the opportunity during their period of training, of carrying out research in his department. Some of them have been inspired by Kenneth to continue in paediatric research. Others have returned to clinical paediatrics with their clinical focus sharpened by the experience. Specifically I may mention the imaginative registrar rotation scheme which Kenneth established with his colleagues, Richard Dobbs, Tony Jackson, and Bertie Webb of Taunton, and in which the registrar spends one out of three years in neonatal research in Kenneth's department. Clinicians enjoy working with Kenneth, in part because he has much clinical experience gained during the war years as physician, including the period spent with the Friends Ambulance Unit in China.

'There is a particular interest of Kenneth's which should be mentioned. Physiologists who use human beings as subjects for their experiments have given much thought to the ethical principles of such research. Claude Bernard in 1865 realised clearly that data obtained from experiments on human beings are essential if the results are to be applied safely to the practice of clinical medicine. But Bernard warned that experiments, however interesting for science and potentially beneficial for the health of others, are not justified if they bring a degree of danger to the subject of the experiment. Robert McCance, the James Spence Medallist of 1961, in a splendid essay on perinatal physiology, points out that during the closing years of the last century and the first 25 years of this, physiologists such as Haldane and Barcroft carried out experiments on humans which would not have satisfied Bernard's criteria because there was some risk. However, these great physiologists, and a little later McCance himself and Widdowson, experimented on themselves and their colleagues. In his work with the newborn Kenneth insists on the strictest ethical criteria and Claude Bernard would have approved. He never sedates a baby in order to facilitate the investigation, he likes the mother to be present during the experiment, and when wishing to obtain the mother's permission for an experiment on her normal baby he does not use the subterfuge that the experiment might help her baby. At the same time he has no doubt, and has convinced all of us, that research on the newborn is an essential ingredient of paediatric research aimed at the improvement of child health.

'In 1974 at the Royal College of Physicians of London he summarised his views on these important matters in a Bertram Louis Abrahams Lecture entitled 'Investigating the newborn infant: the ethical imperative'. The Medical Research Council has been slow in recognising the importance of paediatric research, and facing up to the ethical problems of such research. I am hopeful that the attitude of the MRC is beginning to change in this respect, and if I am right then much of the credit for this enlightment will go to Kenneth who has been engaged in lively debate with the MRC for some time.

'My brief remarks will have made it clear that, like most original minds, Kenneth has had to overcome obstacles. Fortunately he is a fighter. Such a man needs even more than most of us a wife with whom he can share the exasperations arising from professional conflicts or who on other occasions is ready to put up with an irritable temper resulting from the battles of the day. Sheila is all this to Kenneth and so much more. Her own contributions to paediatrics are considerable, and she even finds time to serve our Association with distinction on Council and as Regional Representative. Perhaps from time to time she too comes home in the evening ready to share *her* worries with Kenneth. We wonder who speaks first?

'And now Kenneth may I give you this year's James Spence Medal.'

James Spence Medallists

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Archives of Disease in Childhood, 1979, **54**, 492–498

Physiological responses of the newborn infant to resuscitation

A. W. BOON, A. D. MILNER, AND I. E. HOPKIN

Department of Child Health, and Nottingham City Hospital,

SUMMARY Lung ventilation, endotracheal, and intraoesophageal pressures were measured during standard resuscitation of 20 asphyxiated babies born by caesarean section. The most common response to resuscitation was the production of a large positive intraoesophageal pressure. An opening pressure $>2\cdot0$ kPa was required to expand the lungs of most of these babies. The need for resuscitation was associated with prolonged maternal anaesthesia before delivery.

Endotracheal intubation and IPPV have for many years been the standard methods of resuscitating severely asphyxiated newborn infants. The aim is to expand and ventilate the lungs and to stimulate the infant into spontaneous respiration. Few attempts have been made to evaluate this technique or to study its effects on the neonate. Cross *et al.* (1960) showed that lung inflation in the neonatal period often produces reflex inspiratory efforts—such as, Head's paradoxical reflex. However, Hull (1969) demonstrated that during resuscitation the most common initial response to lung inflation is a reflex expiratory effort.

Pressure and volume studies on isolated newborn lung preparations have demonstrated an 'opening pressure' which has to be exceeded in order to expand the lung (Agostini, 1959; Gribetz *et al.*, 1959; Craig, 1963; Gruenwald, 1963; Rosen and Laurence, 1965). However, Karlberg showed that some spontaneously breathing babies are able to expand their lungs with a small opening pressure (Karlberg and Koch, 1962, Karlberg *et al.* 1962). More recently, Milner and Saunders (1977) showed that this is the most common pattern of lung expansion at birth. We therefore wanted to study the response of the newborn infant to resuscitation and to find out if an opening pressure was exhibited in the lungs of babies requiring resuscitation.

Method

Apparatus. The apparatus used was a Vickers resuscitation trolley with a spring-loaded valve set at 30 cmH$_2$O (2·94 kPa) in the inspiratory line. Oxygen was delivered at a rate of 3 l/min (0·05 l/second) via a modified T-piece (Fig. 1). Inflation pressure was measured using a strain gauge pressure transducer (SE Labs SEM 4–86). Intrathoracic pressure changes were measured using an 8 FG water-filled catheter perfused at a rate of 1 ml/hour using an infusion pump (Sandoz infusion pump). Tidal flow was measured across a pneumotachograph using an Elema-Schönander differential pressure transducer (EMT 32C). The flow signal was fed through an electronic integrator to produce the tidal volume. The oesophageal and inflation

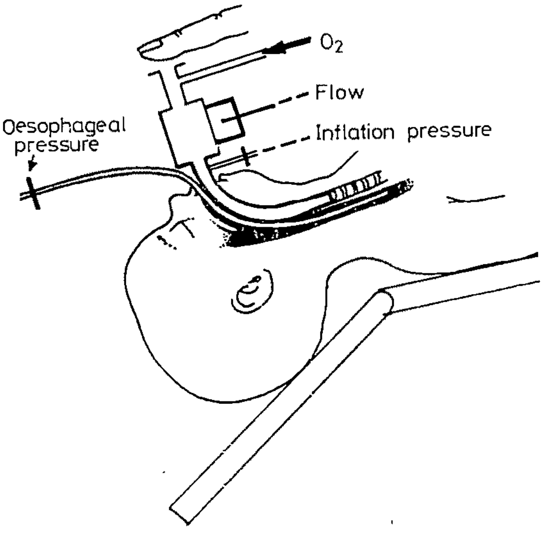

Fig. 1 *Diagrammatic representation of modified T-piece.*

Department of Neonatal Medicine and Surgery, Nottingham City Hospital
A. W. BOON, research fellow
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pressures were calibrated against a water-filled manometer at the end of each run. The flow was calibrated using a rotameter and the tidal volume by injecting a known volume of air through the T-piece. The signals were transferred via an amplification system (SE Emma) to a 4-channel FM tape recorder (SE 84) and simultaneously displayed on a multichannel oscilloscope (SE Labs SEM 430).

Technique. The baby was placed on the resuscitation trolley immediately after delivery. Standard indications for resucitation were used—that is, the infant was apnoeic with a falling heart rate, hypotonic with no response to oropharyngeal suction, and a blue or white colour (Apgar score 3 or less).

A Warne's 14 FG neonatal tube was used routinely. The oesophageal catheter was passed orally while withdrawing the laryngoscope. The tube was passed to a distance of 13 cm from the lips so that the end lay in the lower third of the oesophagus (Milner *et al.*, 1978a). The baby's lungs were inflated at a rate of 30–40/min using an inflation time of approximately 1 second.

Data analysis. The data were analysed in two ways. The output from the tape recorder was fed into a 6-channel recorder with ultraviolet-sensitive paper (SE Oscillograph Se 3006). The inflation pressure and tidal volume signals were also played through an X–Y plotter (SE 225 Mark II) at 25% of the recording speed in order to construct pressure-volume loops of each lung inflation.

The frequency response of the system was assessed by mounting the oesophageal catheter and T-piece with endotracheal tube in a bung which was sealed in a 3-litre container. The open end of the T-piece was occluded and one of the tubes from the pneumotachograph was clamped off. The response characteristics were first determined by injecting 20 ml air rapidly via the T-piece into the container. The response times of the volume and inflation pressure signals were identical. As the limiting factor was the rate of injection of air, a sudden rise in pressure was achieved by bursting an inflated rubber balloon within the container. The 63% rise time of the pneumotachograph and inflation pressure systems were identical at 6·2 milliseconds giving a damping of 3 dB/octave at 25·7 Hz. The 63% rise time of the oesophageal pressure system was 13·2 milliseconds producing a 3 dB/octave attentuation at 11·7 Hz.

Subjects. Recordings were made in a total of 20 asphyxiated neonates born by lower segment caesarean section at a mean birthweight of 3·06 kg and gestation of 39 weeks. The Table gives the clinical details of the infants; 15 of them were delivered by elective caesarean section and 5 by emergency caesarean section. After preoxygenation, general anaesthesia was induced with thiopentone and suxamethonium. Anaesthesia was maintained with nitrous oxide and oxygen, with the addition of halothane in 9 cases, atropine in 4, and pancuronium in 4. Twelve of the babies had gasped or cried before becoming apnoeic.

Table *Clinical details of 20 babies*

Case	*Birthweight (kg)*	*Gestation (weeks)*	*Indication for LSCS*	*Time from general anaesthesia to delivery (min)*	*No. of gasps before intubation*	*Time from intubation to regular respiration (min)*	*Response to inflation*		
							1st	*2nd*	*3rd*
1	3·590	40	Transverse lie	25	0	4	None	None	R
2	4·150	40	Breech	15	3	2	R	R	R
3	2·000	40	Failing placental function	10	0	2½	R/H	None	None
4	3·128	40	Disproportion	13	Cry	4	None	None	None
5	2·980	40	Breech	7·5	1	5	R	R	R/H
6	3·400	37	Diabetic	8	0	3	R/H	R/H	R/H
7	2·740	37	Breech	12	2	2	H	None	None
8	2·940	40	Breech	10	0	4	R	None	R/H
9	2·330	40	Breech	8	3	3	R	R	R
10	2·940	40	Breech	13	1	4	None	None	None
11	1·200	31	Hypertension	8·5	1	2½	H	R	None
12	3·400	39	Transverse lie	11	1	2	R	R/H	H
13	2·910	40	Breech	10·5	1	1½	None	None	H
14	3·990	42	Pre-eclampsia	8	0	3	R	R/H	None
15	3·850	39	Breech	9	2 + cry	3½	R	R	R
16*	3·050	40	Breech	12	Cry	2	R	R/H	R/H
17*	2·800	39	Disproportion	13	0	7	R	R/H	R
18*	3·570	40	Brow presentation	12	0	3	R	None	R
19*	2·720	36	Fetal distress	4·5	1	3	R	R	R
20*	3·460	40	Fetal distress	7	1 + cry	3	R	R	None

*Emergency segment caesarean section, LSCS=lower segment caesarean section, R=rejection response, H=Head's paradoxical reflex.

These subjects were matched for birthweight and gestation with 23 babies born by lower segment caesarean section who did not require resuscitation at birth. The project was passed by the North Nottingham ethical committee.

Results

Responses to lung inflation. The responses of the baby to the first 3 inflations were analysed. In some instances more than one response was seen, therefor the responses add up to more than 60.

Rejection response

The most common response to lung inflation was a large positive intraoesophageal pressure—that is expiratory effort of up to 11 kPa (Figs 2 and 3). This response was seen with 37 inflations. The positive pressure ranged from 13–114 cmH_2O (1·27–11·18 kPa) with a mean of 63·9 cmH_2O (6·26 kPa). This response by the baby frequently caused expulsion of gas from the lungs while the inflation pressure was maintained (Fig. 3).

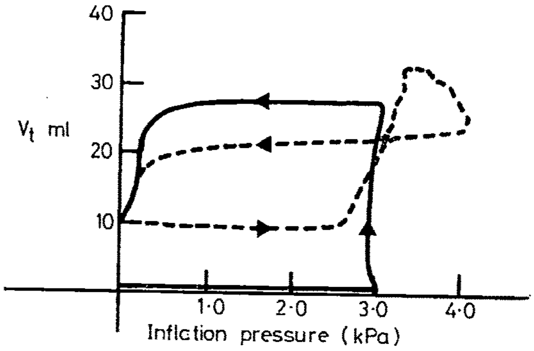

Fig. 3 (*Case 9*). *X–Y plot of inflation pressure against volume. In this and in subsequent X–Y plots, the 1st breath is represented by a solid line and the 2nd by a dashed line. During the 2nd inflation, gas was expelled from the lungs by the baby's 'rejection response'.*

Head's paradoxical reflex

On 15 occasions the infant responded to lung inflation with an inspiratory effort (negative oesophageal pressure)—that is, Head's paradoxical reflex (Figs 4 and 5). The negative pressure produced ranged from 3·6–48cmH_2O (0·35–4·70 kPa) with a mean of 20·1 cmH_2O (1·97 kPa). These inspiratory efforts often produced a fall in inflation pressure, sometimes resulting in negative endotracheal pressures of up to 30 cmH_2O (2·94 kPa) despite a biased flow of 3 l/min.

Passive inflation

On 17 occasions the baby's lungs were inflated with no active change in the oesophageal pressure. The pressure change in these instances was merely being transmitted across the lung (Figs 6 and 7).

On two occasions there was no oesophageal pressure change and no oxygen entered the lungs (Fig. 8).

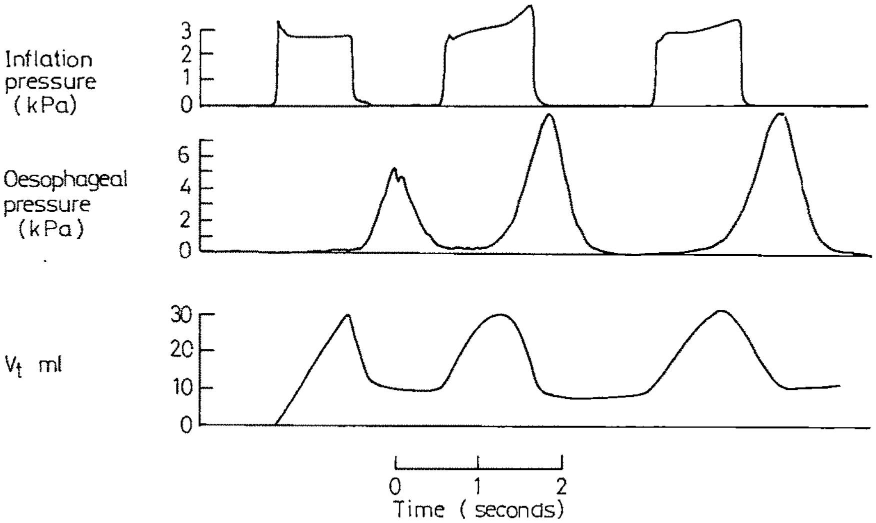

Fig. 2 (*Case 9*). *Inflation pressure, oesophageal pressure, and tidal volume* (V_t) *plotted against time, showing a 'rejection response' to lung inflation. Preinflation oesophageal pressure has been arbitrarily chosen as zero. The baby formed a functional residual capacity* (*FRC*) *of 10 ml.*

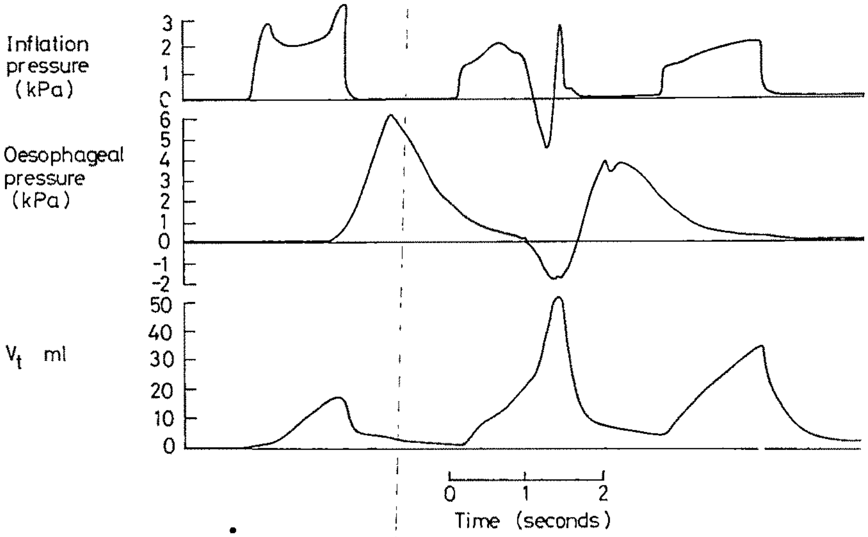

Fig. 4 (*Case 14*). *'Longitudinal trace' showing a rejection response to the 1st inflation with a Head's paradoxical reflex and rejection response to the 2nd inflation. Note the pronounced swings in inflation pressure.*

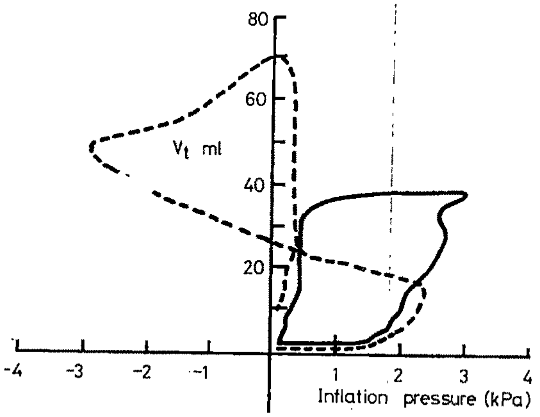

Fig. 5 (*Case 6*). *X–Y plot of inflation pressure against volume. The 2nd inflation was associated with a Head's paradoxical reflex and a pronounced increase in the volume of gas entering the lung. Note the low opening pressure of 1·5 kPa unlike that in Fig. 3.*

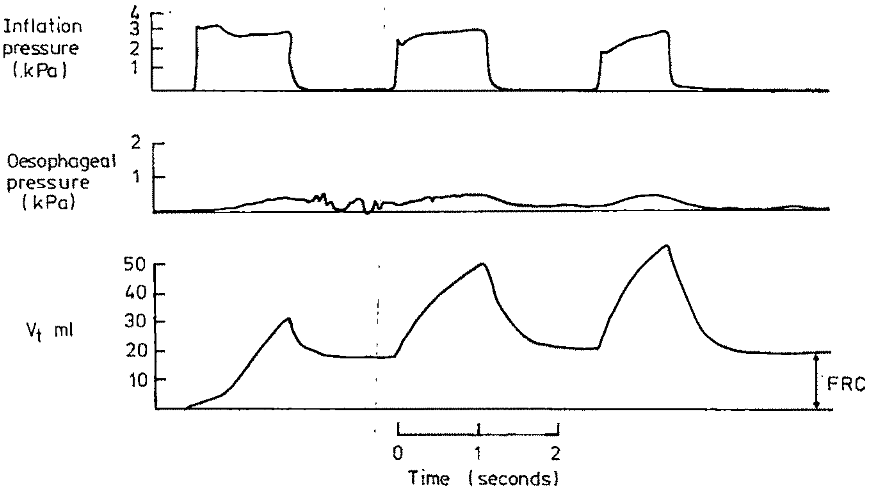

Fig. 6 (*Case 10*). *'Longitudinal trace' showing small passively transmitted changes in oesophageal pressure with each inflation.*

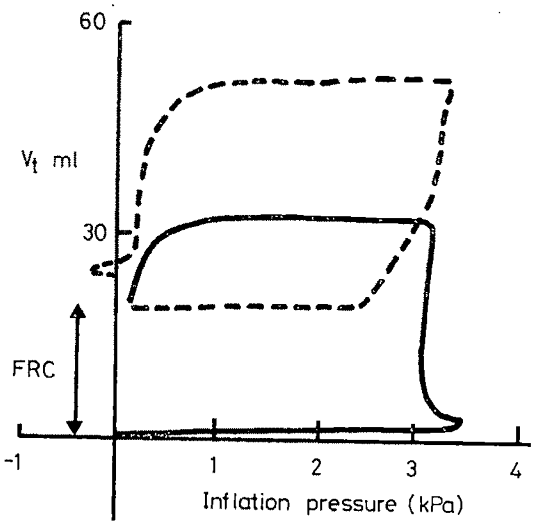

Fig. 7 (*Case 10*). *X–Y plot of the same baby as in Fig. 5. Again, there was an opening pressure in excess of 3 kPa.*

Inflation pressures and volumes during resuscitation. It was only possible to construct pressure/volume loops in 12 of the 20 babies. In the other 8 babies, the initial volume trace was unsatisfactory because of integrator drift and had to be obtained by integrating tidal flow from the tape recordings. Of the 12 babies on whom full data were available, 10 required an opening pressure of 2·0 kPa or more (mean 2·69 kPa) in order to expand their lungs (Figs 3 and 7). Rather surprisingly, 7 of this group had gasped before becoming apnoeic. In 2 infants lung expansion started with a pressure of 1·5 in one and 1·3 kPa in the other (Fig. 5).

Factors affecting the response to lung inflation. The intubated group of babies was compared with 23 matched controls who had a mean birthweight of 3·24 kg and gestation of 39·7 weeks. There was no significant difference in the indication for caesarean section or anaesthetic agents given to the mothers. However, the time from induction of anaesthesia to delivery of the baby was significantly shorter in the control group than in the intubated group (7·82 compared with 10·85 minutes, $P<0·02$). Furthermore, the longer the interval between induction of anaesthesia and delivery of the baby, the fewer the active responses to lung inflation produced by the baby. However, whether the baby had gasped or cried before becoming apnoeic did not predict the baby's response.

Discussion

This study confirms the work of Hull (1969) that the most common initial response to lung inflation is a reflex expiratory effort. It is possible that this large positive intrathoracic pressure represents a cough or a cry, although this is somewhat unexpected in an infant who has previously made little or no response to mucosal stimulation or tracheal intubation. It is obviously impossible to identify, without complicated electromyography, whether this is a cough or cry when the baby is intubated. Only three groups of lung mechanoreceptor are known to be stimulated by lung inflation: (1) pulmonary stretch

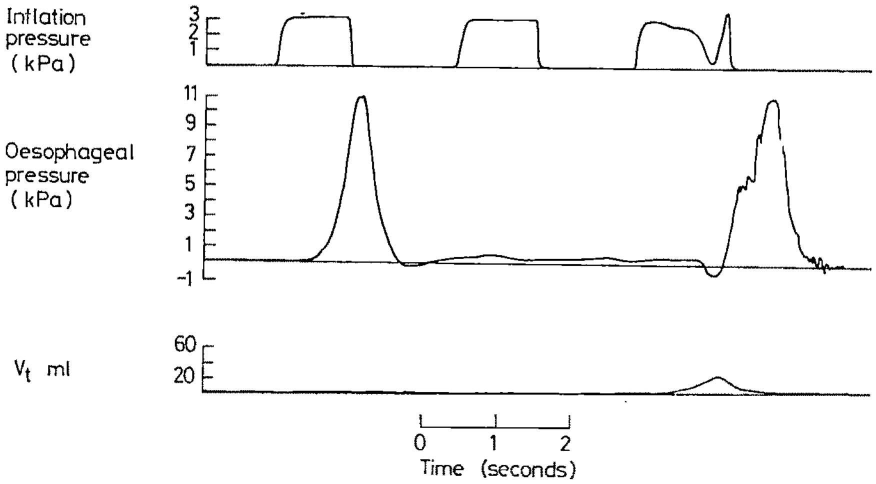

Fig. 8 (*Case 8*). *Longitudinal trace of a baby who showed all four types of responses to the first 3 inflations.*

receptors, which inhibit respiratory activity; (2) nonmyelinated vagal fibres responding to chemicals and large lung inflations to cause apnoea and rapid shallow breathing; (3) lung irritant receptors which normally cause a gasp (Coleridge *et al.*, 1965; Mills *et al.*, 1970; Sellick and Widdicombe, 1970). However, direct stimulation of the irritant receptors in newborn infants frequently causes apnoea or slowing of respiration (Fleming *et al.*, 1978). It is of interest that reinflation of a collapsed lung in healthy adults sometimes causes a cough (Burger and Macklem, 1968). It seems possible that this response is mediated via pulmonary irritant receptors.

Whatever the mechanism of the response, it was seen less often in the more severely asphyxiated babies and in those infants in whom there had been a particularly long interval between the induction of anaesthesia and delivery of the infant. It is interesting that spontaneously breathing babies who were not intubated also commonly produce large intrathoracic pressures on their first expiration (Karlberg *et al.*, 1962; Milner and Saunders, 1977). It is therefore unlikely that this effect is merely caused by the stimulus of cold gas on the respiratory epithelium.

Like Hull (1969) we have shown that Head's paradoxical reflex is seen less often in the initial lung inflation during resuscitation. It was of interest that the baby's own inspiratory efforts were often much more efficient in causing lung expansion than the inflating pressure (Fig. 4). It is not possible to say whether these responses are those of the normal asphyxiated neonate or whether there has been a modification of the response caused by the anaesthetic agent used.

Despite using what is normally accepted as an adequate flow rate of oxygen of 0·05 l/second (3 l/min) (Hull, 1969; Robinson, 1977), the baby's own inspiratory efforts frequently produced large fluctuations in the inflation pressure. It is possible that these large and rapid pressure swings may predispose the infant to develop a pneumothorax and for this reason it may be that higher flow rates of oxygen should be used to lessen this possibility.

It appears from these data that, unlike spontaneously breathing infants, babies requiring resuscitation at birth exhibit an opening pressure remarkably similar to 20 cmH_2O (1·96 kPa) calculated on theoretical grounds by Avery and Mead (1959) and found by workers inflating isolated lungs (Agostini, 1959; Gribetz *et al.*, 1959; Craig, 1963; Gruenwald, 1963; Rosen and Laurence, 1965). It is unlikely that the opening pressures we demonstrated are artefactual, as the frequency response of the inflation pressure and pneumotachograph systems was identical.

One possible reason for this opening pressure difference between spontaneously breathing and resuscitated babies may be that the baby's own efforts are more efficient at expanding the lungs as the force is being applied from all around the lungs.

Another factor which may account for the higher opening pressures in resuscitated babies may be that they were all born by lower segment caesarean section and therefore had not benefited from the effects of vaginal delivery in expressing liquid from the lungs (Milner *et al.*, 1978b) or from any other changes as the baby passes down the birth canal. It is unlikely that the pressure differences are due to the presence or absence of surfactant as none of the resuscitated babies developed any respiratory distress.

To try to clarify this difference we now intend to study vaginally-born babies requiring resuscitation at birth.

Conclusion

We feel it is important to state that there is still no way of predicting clinically which apnoeic babies are severely asphyxiated and whether they will produce active responses to resuscitation. Furthermore, babies who had cried or gasped at birth did not appear to differ from the group as a whole and sometimes produced no responses (for example, Cases 4 and 10). Intubation and IPPV should therefore continue to be the standard method of resuscitating apnoeic neonates.

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Metabolic and hormonal responses of low birthweight infants to intravenously infused calories not exceeding the maintenance energy expenditure

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SUMMARY Eight low birthweight infants were studied for their metabolic and hormonal responses to intravenous alimentation when the caloric input was varied. The study was made during three consecutive 12-hour periods, when solutions of glucose, glucose and amino-acids, and glucose and amino-acid and lipids were successively infused. Hypertonic glucose led to a fall in plasma free fatty acids and amino-acids. Supplementation with an amino-acid mixture increased the concentration of amino-acids but not above the fasting level. Thus, hypertonic glucose was an effective means for avoiding hyperaminoacidaemia. Blood urea was little changed, also indicating satisfactory use of amino-acids. The number and distribution of calories infused throughout the third 12-hour period, when lipid was infused, were also important factors contributing to the avoidance of hyperaminoacidaemia. The caloric needs of low birthweight infants kept at neutral temperatures should be individually assessed in the light of recent data. The administration of an unnecessarily large load of calories and nutrients to parenterally-fed infants can thereby be avoided.

Knowledge of the caloric expenditure of the newborn infant, and of the factors which may alter it, is essential when alimentation is given by the parenteral route. Thus, if preterm infants <1500 g are fed intravenously using conventional estimates of maintenance energy expenditure, an excessive caloric load may be imposed leading to dangerous complications. These estimates often fail to take account of the fact that maintenance caloric requirement in the neonatal and postneonatal periods varies greatly according to weight, and gestational and postnatal ages (Mestyán *et al.*, 1968; Rubecz *et al.*, 1974; Rubecz and Mestyán, 1975). In view of this, we investigated the changes in the levels of the main plasma metabolites after infusion of nutritive mixtures with a low caloric value appropriate to the relatively low energy needs of low birthweight infants. The results may serve as a basis for further studies to define the caloric aspects of total parenteral nutrition in such infants.

Materials and methods

Infants. Eight low birthweight infants (2 appropriate for and 6 small for gestational age), in whom early oral feeding had failed, were infused with nutritive solutions for 36 hours. The mean gestational age was 32 weeks (range 28–35) and the mean birthweight 1362 g (range 900–1930). The average postnatal age at which parenteral feeding began was 18 hours. Clinical data, the volume of the nutritive solutions, and the calories and amounts of glucose, amino-acids, and lipid infused are summarised in Table 1.

Infusions. The design of the short-term IV feeding was as follows: (1) 10% glucose was given for 12 hours; (2) during the second 12-hour period 10% glucose with 2·7% crystalline amino-acids (Aminosol 2400: Vitrum, Stockholm) was infused; (3) thereafter in addition to the glucose and amino-acid mixture, 10% lipid solution (Intralipid: Vitrum, Stockholm) was infused by a second pump connected through a Y-connection. In this third 12-hour period when a mixture of the three main nutrients was given, care was taken not to exceed appreciably the maintenance energy expenditure. The supplementation of glucose

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Table 1 *Clinical data of 8 infants, volume of fluid, amount of calories and nutrients infused*

Case	*Gestational age (weeks)*	*Birth-weight centile*	*Birth-weight (g)*	*Postnatal age (hours)*	*Rate of infusion (ml/kg per min)*			*Caloric input (kcal/kg per day)*			*Nutrients infused (g/kg per day)*					
					Glucose	*Glucose + amino-acids*	*Glucose + amino-acids + lipid*	*Glucose*	*Glucose + amino-acids*	*Glucose + amino-acids + lipid*	*Glucose*	*Glucose + amino-acids*		*Glucose + amino-acids + lipid*		
											Glucose	*Glucose*	*Amino-acids*	*Glucose*	*Amino-acids*	*Lipid*
1	31	<10	1070	44	0·046	0·046	0·065	26·90	33·28	62·88	6·72	6·72	1·44	6·72	1·44	2·68
2	35	10–25	1900	12	0·052	0·052	0·078	30·30	37·00	78·68	7·60	7·60	1·64	7·60	1·64	3·78
3	28	<10	900	4	0·055	0·055	0·077	32·00	39·08	74·28	8·00	8·00	1·72	8·00	1·72	3·20
4	28	<10	990	4	0·050	0·050	0·070	29·08	35·52	70·72	7·26	7·26	1·56	7·26	1·56	2·90
5	35	<10	1720	6	0·058	0·058	0·087	33·48	40·88	86·92	8·36	8·36	1·80	8·36	1·80	4·18
6	35	10–25	1930	6	0·052	0·052	0·077	29·84	36·44	77·46	7·46	7·46	1·60	7·46	1·60	3·72
7	32	<10	1230	35	0·040	0·040	0·057	23·40	28·58	54·32	5·84	5·84	1·26	5·84	1·26	2·34
8	32	<10	1160	35	0·043	0·043	0·060	24·82	30·30	57·60	6·20	6·20	1·34	6·20	1·34	2·48
Means			1362	18·2	0·049	0·049	0·071	28·72	35·13	70·35	7·18	7·18	1·54	7·18	1·54	3·16

1 kcal ≈ 4·2 kJ.

as the basic caloric source, first with amino-acids and then with fat emulsion, represented a short-term alimentation programme with increasing caloric input and changing composition of the nutritive mixture. In brief, the study consisted of three consecutive 12-hour periods during which solutions containing glucose, glucose and amino-acids, and glucose and amino-acids and lipids, were infused.

Chemical and hormonal monitoring. Blood samples were drawn through an umbilical venous catheter before IV nutrition and at the end of each infusion period. The following metabolites were measured: glucose (Pryce, 1967), free fatty acids (Dalton and Kowalski, 1967; Laurell and Tibbling, 1967), lactate (Huckabee, 1958), α-amino-nitrogen (Rubinstein and Pryce, 1959), and urea (Ceriotti, 1971). In 6 infants the plasma concentrations of 17 individual amino-acids were also determined using a Beckman automatic amino-acid analyser. Plasma insulin and growth hormone were estimated (Hunter and Greenwood, 1962; Hales and Randle, 1963). Means and standard errors were calculated, and significance was estimated by the paired Student's *t* test.

Results

Response of blood glucose, lactate, and plasma FFA. Fig. 1 shows that the concentrations of glucose at the end of the three infusion periods were higher than the control level ($P<0\cdot01$ and $<0\cdot05$). The greatest rise was during the first 12-hour period when only 10% glucose was infused. Thereafter the addition of an amino-acid mixture to 10% glucose resulted in a fall in blood glucose, which remained still significantly above that of the preinfusion level ($P<0\cdot05$). Further supplementation with 10% lipid solution did not greatly influence blood glucose concentration which remained near the level of the end of the glucose and amino-acid period.

The mean concentration of plasma free fatty acids (FFA) fell in response to 10% glucose but, owing to the large individual variation of the fasting level, the fall was not significant. The infusion of amino-acids in addition to glucose caused a further decrease in the plasma FFA. Supplementation with 10% lipid solution, as expected, was associated with a pronounced rise in FFA concentration ($P<0\cdot01$).

Mean blood lactate was slightly raised by the end of the 10% glucose period. Supplementation with amino-acids and fat emulsion induced a gradual fall in blood lactate. However, its concentration by the end of the third infusion period, owing to the large variation in the starting values, was again not significantly lower than that before IV nutrition.

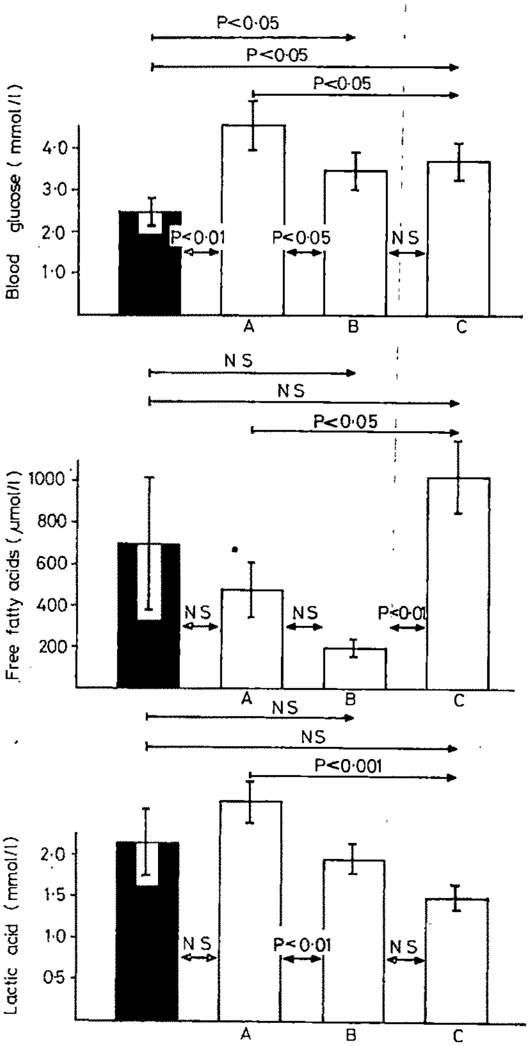

Fig. 1 *Response of blood glucose, free fatty acids, and lactic acid to infusions of* (*A*) *10% glucose,* (*B*) *10% glucose + 2.7% amino-acid, and* (*C*) *10% glucose + 2.7% amino-acid + 10% lipid.*

Changes in the plasma α-amino-nitrogen, urea, and amino-acid pattern. The changes in α-amino-nitrogen and urea content of the plasma are shown in Fig. 2. The mean level of α-amino-nitrogen fell significantly in response to 10% glucose ($P<0{\cdot}05$), but regained the fasting level when an amino-acid mixture was added to glucose. Further supplementation with 10% lipid solution did not affect the level, which remained at the fasting value.

Mean urea nitrogen was not greatly affected, with only a slight tendency to rise during the second and third 12-hour periods when the amino-acid mixture was given.

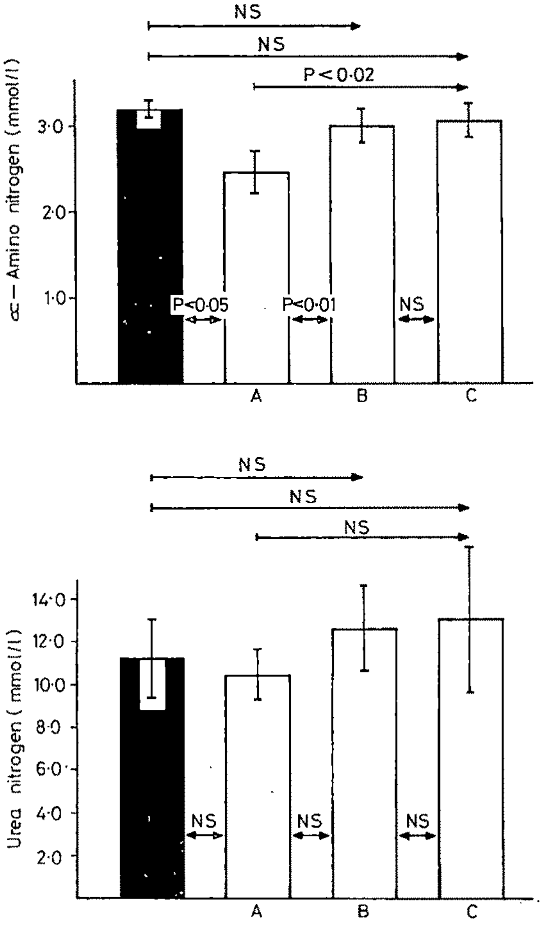

Fig. 2 *Plasma α-amino-nitrogen and urea nitrogen during infusion of* (*A*) *10% glucose,* (*B*) *10% glucose + 2.7% amino-acid, and* (*C*) *10% glucose + 2.7% amino-acid + 10% lipid.*

Unfortunately only 2 of the 6 infants in whom there were changes in the plasma concentration of 17 different amino-acids were tested before parenteral nutrition. However, from previous observations (Rubecz *et al.*, 1974) we know that glucose infusion causes a pronounced fall in most individual amino-acids, and the same response of the plasma α-amino-nitrogen was seen in our study. The hypoamino-acidaemic effect of 10% glucose is also evident if the combined fasting concentration of the 17 amino-acids obtained in the 2 infants (2673 µmol/l) is compared with that obtained by the end of the 10% glucose period in 6 infants (1559 µmol/l). The

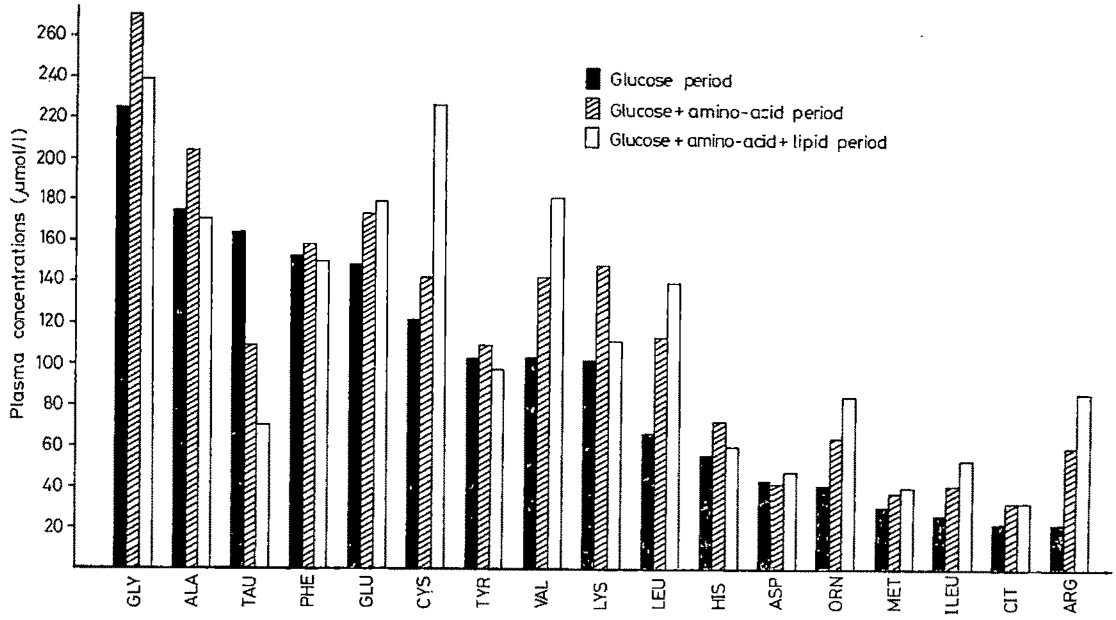

Fig. 3 *Concentrations of individual plasma amino-acids during the three intravenous nutrition regimens.*

responses of the individual amino-acids in the second and third 12-hour periods of intravenous nutrition are shown in Fig. 3. Owing to the small number of infants in whom each of the 17 amino-acids could be followed throughout the three infusion periods, statistical analysis was not made, but 13 amino-acids clearly increased their plasma concentrations when glucose was supplemented with amino-acid solution. The rise of phenylalanine, tyrosine, and asparagine was negligible. It is interesting that one amino-acid, taurine, responded to the addition of the amino-acid by a pronounced fall.

By the end of the third infusion period, when fat was added to the glucose and amino-acid mixture, a further rise was observed in the levels of 8 amino-acids (glutamine, cystine, valine, leucine, ornithine, methionine, isoleucine, and arginine), with no change or fall in the concentration of glycine, alanine, tyrosine, lysine, histidine, asparagine, citrulline, and phenylalanine. Among those amino-acids whose concentration decreased in response to lipid, in none did the concentration fall below that at the end of the first infusion period. Taurine, however, showed a further pronounced fall when glucose and amino-acid was supplemented with lipid.

Insulin and growth hormone response. The mean responses of plasma insulin and growth hormone (GH) are shown in Table 2. By the end of the 10% glucose period the mean plasma level had increased. The addition of amino-acid mixture to the infusate caused a further increase in the mean level of both hormones. By the end of the third period plasma insulin and GH mean levels were both lower.

It should be noted that the magnitude and the time course of individual insulin response (Fig. 4) showed

Table 2 *Effect of glucose, glucose + amino-acid, and glucose + amino-acid + lipid infusion on plasma growth hormone and insulin concentration*

		Before intravenous infusion	*After 10% glucose*	*After 10% glucose + 2·7% amino-acid*	*After 10% glucose + 2·7% amino-acid + 10% lipid*
Insulin (μU/ml)	Mean ± SE	9·7 ± 2·2	20·3 ± 5·4	29·8 ± 13·6	24·7 ± 11·9
		P<0·05			
Growth hormone (ng/ml)	Mean ± SE	19·0 ± 2·1	51·6 ± 7·1	65·2 ± 4·0	33·6 ± 4·2
		P<0·01			

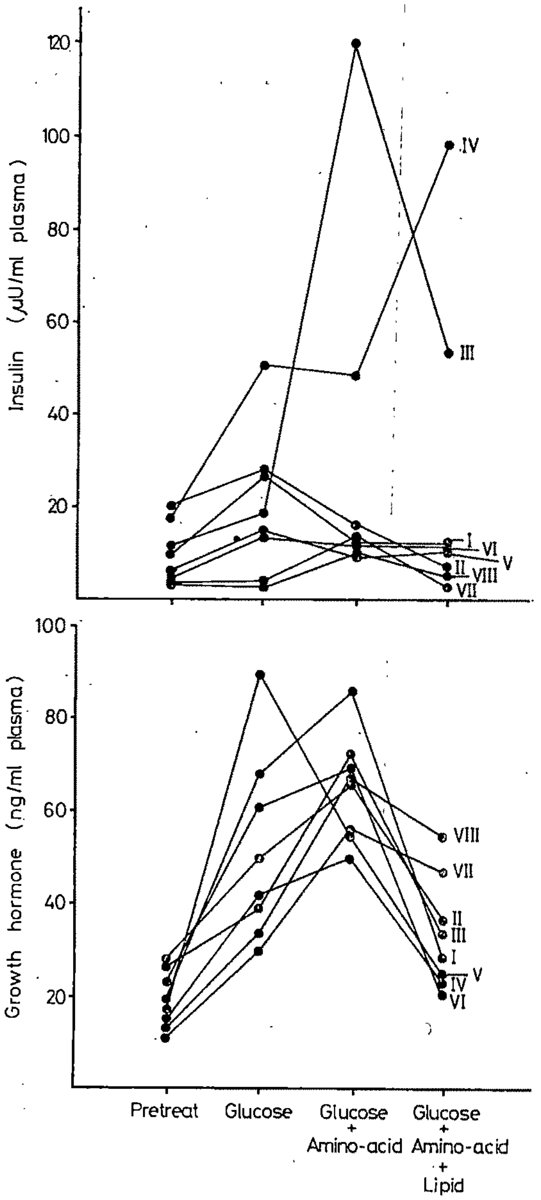

Fig. 4 *Plasma insulin and growth hormone during the glucose, glucose + amino-acid, and glucose + amino-acid + lipid infusions to 8 infants.*

much variation. The changes in GH were more uniform. The definite increase elicited by 10% glucose was followed by a further pronounced increase in response to the combined infusion of glucose and amino-acids, when addition of lipid was associated with a pronounced fall.

Discussion

It has been shown that the basal metabolic rate of small infants and the total daily heat production is considerably less (Mestyán *et al.*, 1968; Rubecz and Mestyán, 1975) than that predicted by Gordon and Levine (1936). The three levels of caloric intake (lower, equal, and higher than the basal requirement) represented by the three infusion periods were chosen to take account of this newer information.

Changes in blood glucose and FFA. As in our previous observations (Rubecz *et al.*, 1974) hypertonic glucose infusion caused a rise in blood glucose and a fall in plasma FFA. The fall in FFA became more pronounced by addition of the amino-acids to 10% glucose, but blood glucose was much lower. As expected, the addition of fat emulsion led to a substantial rise in plasma FFA, blood glucose remaining unchanged.

Responses in plasma amino-acids and urea level. The hypoaminoacidaemia observed by the end of the 10% glucose period is in accordance with the known interrelationship between carbohydrate and amino-acid metabolism (Munro and Thomson, 1953). The removal of amino-acids from the plasma as shown by the fall in α-amino-nitrogen content was significant. It is noteworthy that the rise in plasma α-amino-nitrogen after amino-acid supplementation did not exceed the fasting level. This confirms our previous finding (Rubecz *et al.*, 1974) that administration of hypertonic glucose is an effective means of avoiding hyperaminoacidaemia, a potentially dangerous consequence of infusing amino-acid mixtures. It is also significant that the normal total plasma amino-acid level was maintained during the third 12-hour period when lipid was infused in addition to the glucose and amino-acid solution.

Supplementation with amino-acid mixture increased the plasma concentrations of most individual amino-acids. The increment was variable and seemed to reflect the composition of the amino-acid solution infused. Taurine was the only amino-acid where plasma level fell throughout the infusion periods. The infusion of lipid in addition to glucose and amino-acids altered the plasma amino-acid pattern appreciably.

The fact that blood urea was practically unchanged indicated that the amount of amino-acids infused did not cause a rate of urea production which exceeded the renal excreting capacity. In view of the possibly increased amino-acid transport to tissues due to stimulated insulin secretion (Kipnis and Noall, 1958) it appears reasonable to assume that the anabolic use of amino-acids was also improved when the caloric input, and hence the amino-acid load, did not exceed the maintenance energy expenditure.

Changes in plasma insulin concentration. The magnitude and time course of the individual changes in plasma insulin were found to be variable. This particularly applied to the glucose period when a marked or a moderate response was observed or sometimes none. This is consistent with reports which point out that the insulin response to a glucose load in either normally grown or growth-retarded low birthweight infants is generally poor, particularly within the first 48 hours of life (Baird and Farquhar, 1962; Milner and Hales, 1965; Grasso *et al.*, 1968; Gentz *et al.*, 1969). The change of plasma insulin after supplementation of glucose with amino-acids was also found to be variable: it either elicited a small rise in infants in whom glucose was ineffective, or maintained the moderate increase caused by glucose infusion. In two infants it even abolished the glucose-stimulated insulin secretion. These observations are in accordance with the observations of Pildes and Wong (1973) and with our previous study (Rubecz *et al.*, 1974) in which administering amino-acids in addition to glucose failed to enhance insulin secretion. The low birthweight, immaturity, and pathological conditions of infants included in the previous and present studies may be a relevant factor in explaining the lack of synergism between glucose and amino-acids, and the inconsistent pattern of insulin response.

Although direct evidence for an effect of plasma FFA on insulin secretion in man is lacking, FFA have been shown to stimulate insulin secretion in the dog (Crespin *et al.*, 1969). In the present investigations lipid did not seem to modify consistently the plasma insulin content, which either remained unchanged or fell to the fasting level. In only one infant was a further appreciable increase observed. Asch *et al.* (1975) reported a somewhat higher (but nonsignificant) insulin level in infants in response to a 12% glucose +2·5% amino-acid and 10% soybean oil emulsion parenteral nutrition regimen, compared with the infusion of a mixture of 12% glucose and 2·5% amino-acid solution.

Changes in plasma growth hormone concentration. Unlike the changes in plasma insulin, the response of GH was more uniform. In all infants but one, the response induced by 10% glucose was further increased by the supplementation with amino-acids. It is well known that in newborn infants glucose induces GH release, and amino-acids—such as arginine—are also potent stimuli (Stubbe and Wolf, 1970; Le Dune, 1972; Stubbe *et al.*, 1973). It is interesting that further supplementation with lipid depressed GH level in most infants, in some it completely abolished the response elicited by glucose and glucose amino-acids. In adults (Blackard *et al.*, 1971), and in rhesus monkeys (Blackard *et al.*, 1969), the administration of corn oil emulsion and heparin suppressed insulin and arginine-induced GH secretion, and it was suggested that this effect might have been due to the FFA component. It is conceivable that in the present study the pronounced rise in plasma FFA concentration in response to lipid supplementation was mainly responsible for the inhibition of stimulated GH secretion.

Besides the changes in hormonal status the administration of lipid was also associated with alterations in the plasma aminogram: the concentrations of a number of amino-acids increased. As GH is known to augment the amino-acid uptake of the tissues (Snipes, 1968) it is reasonable to assume that the raised levels of some amino-acids in response to lipid was the result of suppression of GH secretion.

Conclusions

In view of recent estimates of the maintenance caloric need of low birthweight infants kept at a neutral temperature (Mestyán *et al.*, 1968; Rubecz and Mestyán, 1975) the calories infused throughout the third 12-hour period were, in all probability, high enough to cover maintenance energy expenditure and low enough to avoid undesirable metabolic complications. The distribution of calories of the infusate appears also properly balanced as far as the plasma metabolic profile is concerned. The lack of pronounced biochemical distortions indicate that the pattern of substrate use is also less unphysiological than might be expected with a caloric input much exceeding heat production.

It is time to re-evaluate the energy side of parenteral feeding in low birthweight infants. An individual approach to the estimation of the caloric need for maintenance must be adopted. The components of total heat production (basal metabolic rate, specific dynamic action, activity, thermoregulatory heat production) may vary considerably according to maturity, postnatal age, feeding, and thermal conditions. These factors require individual assessment if the caloric requirement of an individual infant is to be determined.

It is also important to know whether parenteral feeding is to cover maintenance substrate and energy requirements, or is to provide additional calories for growth. In view of the usual absence of growth in low birthweight neonates during the first 10 days of life, it appears unnecessary to increase the caloric input above the maintenance requirement, otherwise most of the extra calories and substrates would probably be rapidly oxidised rather than incorporated in the body tissues.

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Mycoplasma pneumoniae infection

A follow-up study of 50 children with respiratory illness

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SUMMARY Fifty children with a previous history of *Mycoplasma pneumoniae* respiratory tract infection were assessed clinically, and pulmonary function tests carried out after an interval ranging from 1½ to 9½ years (median 2½). 23 suffered from recurrent wheezy bronchitis or asthma, and in 5 the index illness appeared to precipitate the wheezing tendency. All were symptom-free when respiratory function tests were performed. Simple tests of ventilatory function (PEFR, FEV, and FVC) were within normal limits. Increased bronchial reactivity after exercise (a fall in PEFR $>15\%$ resting value) was demonstrated only in children known to have asthma. Maximum expiratory flow rates in air at 50% of vital capacity ($\dot{V}\,max_{50}$) were within the normal range in all patients with the exception of two. The response in flow rate at 50% of vital capacity after inhalation of an 80% helium and 20% oxygen mixture ($\Delta\dot{V}\,max_{50}$) was reduced ($P<0{\cdot}001$) in asymptomatic patients with a history of *M. pneumoniae* respiratory infection, when compared with normal data from 48 healthy schoolchildren without a background of significant respiratory illnesses. These findings indicate impairment of small airways function, even in totally symptom-free children in the study group.

The clinical manifestations of *Mycoplasma pneumoniae* infection in children have been extensively reviewed (Baernstein *et al.*, 1965; Glezen *et al.*, 1967; Fernald *et al.*, 1975; Stevens *et al.*, 1978; Mok *et al.*, 1979). The clinical course of infections caused by this organism is usually self-limiting whether or not the child has had an effective antibiotic. Studies of pulmonary function after *M. pneumoniae* infection in adults show functional abnormalities both in the acute stage (Dierckx and Gillard, 1976) and after clinical and radiological recovery (Berven, 1962). In children with respiratory symptoms studies have been confined to the acute phase of illness (Kjellman, 1976), and we have been unable to find information on pulmonary function status after clinical and radiological recovery. We report here our findings in 50 children with proved *M. pneumoniae* infection studied 1½ to 9½ years (median 2½) after their index respiratory illnesses.

Patients and methods

Patients. The names of all children admitted to the Royal Hospital for Sick Children in Edinburgh with *M. pneumoniae* infection during the period from January 1968 to December 1975 were obtained from the records of the Regional Virus Laboratory in Edinburgh. The case records of 103 children were then traced and analysed. 87 with respiratory illnesses were chosen for further follow-up study. Letters were sent to their parents requesting cooperation. Of 57 replies received, 5 declined and 2 did not attend for study. We did not attempt to trace the remaining 30 patients.

Fifty children (20 girls and 30 boys) aged 0·4 to 11·3 years (median 4) at the time of the index illness were studied after an interval of 1½ to 9½ years (median 2½). Chest *x*-rays obtained during the acute phase of illness showed pneumonic consolidation in 19 (16 involving one lobe and 3 more than one lobe), patchy infiltration in 19 (unilateral in 8 and bilateral in 11), and hyperinflation in 2. In the 10 remaining patients with normal chest *x*-rays, cough was the main presenting symptom.

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Plan of investigation. A clinical questionnaire on each child was completed by one of us (J.Y.Q.M.). Any history of a previous respiratory illness (acute bronchiolitis, whooping cough, pneumonia, measles or chickenpox with chest involvement, or tuberculosis) and/or ongoing symptoms (cough, wheeze, breathlessness, or sputum production) before or after the index illness was noted. Each child was then examined and respiratory function tests carried out in those old enough to co-operate.

With the patient standing, peak expiratory flow rate (PEFR) was measured using the Wright's peak flow meter (Wright and McKerrow, 1959). The best of 3 attempts was accepted. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured using the Vitalograph spirometer, and the FEV_1/FVC ratio calculated.

Maximum expiratory flow volume (MEFV) curves were obtained breathing air followed by an 80% He/20% O_2 mixture. Each child was seated and breathed quietly through a mouthpiece and an attached Lloyd valve. The subject exhaled to residual volume and then performed 3 vital capacities (VC), first breathing air and then the He/O_2 mixture. During the 3rd VC manoeuvre, the child expired forcibly and completely into a 'bag and box' arrangement. Displaced air passed through a flow meter (Mercury Electronics, Scotland Ltd, Glasgow). A linear relationship between flow and output voltage was achieved electronically (Tau Electronics Ltd, Edinburgh). Linearity was checked each week and remained remarkably constant. Volume was obtained from the linearised flow signal using an integrator (Tau Electronics Ltd, Edinburgh). The pneumotachygraph was calibrated for air flow using a rotameter (GEC-Elliott, Process Instruments Ltd, Croydon). A volume calibration was carried out before each study using a 1-litre (BTPS) syringe. An identical volume signal was obtained for flow rates up to 500 l/min. MEFV curves were obtained by displaying flow against volume on the x-y coordinates of a storage oscilloscope (Tektronix Inc., Beaverton, Oregon). An electronic time marker indicated FEV_1. The curves were then photographed and analysed. Previous studies on normal children (H. Simpson, 1977, unpublished observations) had shown that observed differences between curves were independent of the order in which gases were inspired. Curves were compared when the vital capacity breathing He and O_2 was within 5% of that obtained in air. The variables measured were FEV_1, FVC, maximum expiratory flow rates at 50% of VC ($\dot{V}\ max_{50}$) and 25% of VC ($\dot{V}\ max_{25}$) for both the air and He/O_2 curves. The change in flow rate after inhalation of the He/O_2 mixture was measured at both 50 and 25% of VC ($\Delta\ \dot{V}\ max_{50}$ and $\Delta\ \dot{V}\ max_{25}$ respectively).

Patients with a resting PEFR >70% of predicted for height were exercised on a treadmill (Quinton Instruments, Seattle, Washington) for 6 minutes at a speed of 5 km/h at a gradient of 20%. The heart rate was measured after exercise and in each case was at least 160/min. PEFR was measured before exercise, then immediately and at 2, 5, 10, 15, and 30 minutes after cessation of exercise. The percentage fall in PEFR from the resting value was then calculated (fall in PEFR/resting PEFR) × 100.

Results

Clinical. An analysis of case records and clinical questionnaires showed a history of bronchiolitis,

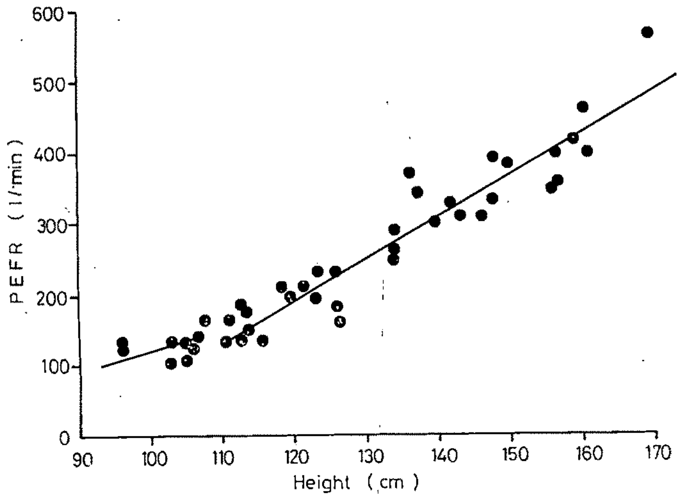


Fig. 1 *Peak expiratory flow rate in 43 children with previous* M. pneumoniae *respiratory infection.*

pneumonia, whooping cough, measles, or chickenpox with chest involvement antedating the mycoplasma illness in 17 children. After recovery, 8 remained symptom-free. Nine had recurrent wheeziness, 8 of them since infancy. 33 children had no specific antecedent illnesses. 19 were symptom-free and 14 had a wheezing tendency which predated the index illness. Six children developed persistent cough or wheeze for the first time after the mycoplasma illness. Five of these (all with recurrent wheeze) had a strong personal or family history of atopic disorders (eczema, food allergy, allergic rhinitis).

On examination 4 children were <10th centile for height and weight and 17 had mild to moderate degree of chest deformity. All patients were symptom-free and had no clinical signs of airways obstruction when respiratory function tests were performed.

Respiratory function tests. Fig. 1 gives the results of PEFR in relation to the normal data of Polgar and Promadhat (1971) and Milner and Ingram (1970). PEFR exceeded 70% of the predicted for height in all but one child. The results of FEV_1 and FVC were within normal limits, compared with the data of Polgar and Promadhat (1971). The FEV_1/FVC ratio expressed as a percentage was 85·1 (±7·8). When patients with wheezy bronchitis or asthma were excluded this ratio was 86·7 (±8·0).

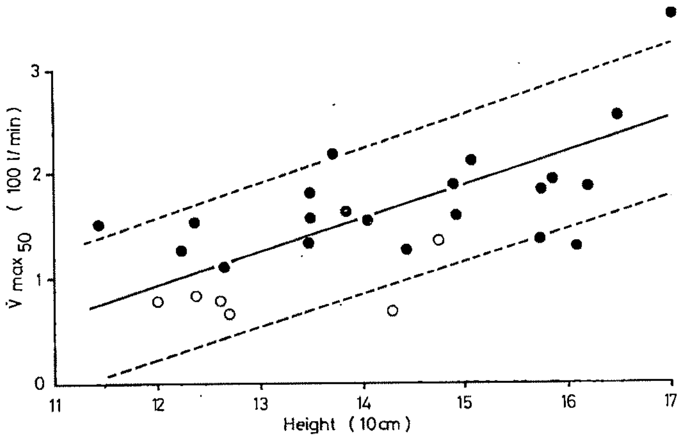
MEFV curves breathing air and then a He/O_2 mixture were obtained in 28 children. 18 had been symptom-free both before and after their index illnesses, 4 had occasional mild wheeze, and 6 were known asthmatics. The results were analysed and compared with 'normal' values obtained in 48 schoolchildren of similar heights and age range but without antecedent lower respiratory tract infections or wheezing tendency. No difference was seen with respect to FEV_1 and FVC between the study and control groups.

Figs 2 and 3 show that in all but 2 patients, the results obtained for $\dot{V}\,\mathrm{max}_{50}$ and $\dot{V}\,\mathrm{max}_{25}$ were within or above the normal range for controls. Figs 4 and 5 show the results for $\Delta\dot{V}\,\mathrm{max}_{50}$ in the control and non-asthmatic patients within the study groups. $\Delta\dot{V}\,\mathrm{max}_{50}$ varies widely even in normal healthy children but in most cases exceeds 20 l/min. Table 1 gives the mean values ±SD for $\Delta\dot{V}\,\mathrm{max}_{50}$ and $\Delta\dot{V}\,\mathrm{max}_{25}$ in our controls and the 22 patients studied who did not have asthma. The $\Delta\dot{V}\,\mathrm{max}_{50}$ of 12·6 ± 13·7 l/min in our study group differed significantly ($P<0{\cdot}001$) from 24·4 ± 20·8 l/min in our controls. The 22 patients included 4 in whom chest *x*-rays were normal during their index illnesses. The values for $\Delta\dot{V}\,\mathrm{max}_{50}$ in these patients were 5, 10, 10, and 25 l/min. When our results were reanalysed, excluding data from these patients, significance remained unaltered. There was no relation between $\Delta\dot{V}\,\mathrm{max}_{50}$ or $\Delta\dot{V}\,\mathrm{max}_{25}$ and height in either the control or study group.

Table 1 *Response in flow at 25 and 50% of vital capacity after breathing a mixture of helium and oxygen* ($\Delta\dot{V}$ *max*$_{25}$ *and* $\Delta\dot{V}$ *max*$_{50}$ *respectively)—actual values ± SD for control and study groups (excluding children with asthma)*

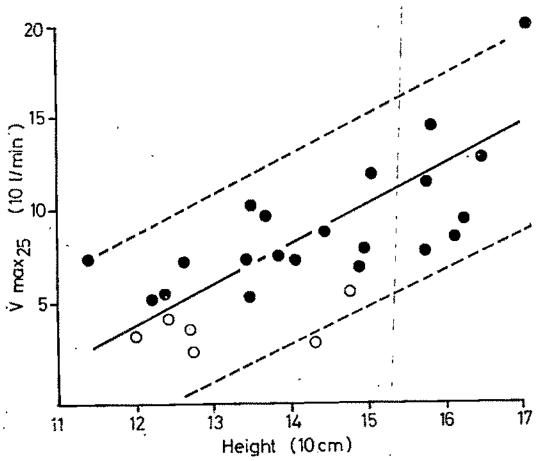
Variable	*Control (Mean ±SD)*	*Mycoplasma (Mean ±SD)*	*Significance*
Height (cm)	140·6 ± 11·4	142·9 ± 17·1	NS
$\Delta\dot{V}\,\mathrm{max}_{25}$	11·5 ± 14·3	8·3 ± 14·2	NS
$\Delta\dot{V}\,\mathrm{max}_{50}$	24·4 ± 20·8	12·6 ± 13·7	P<0·001*

*Wilcoxon test.



(Slope = 3·27 ± 0·22, y intercept = −297·8 ± 31·1, R = 0·73).
● Nonasthmatic patients
○ Asthmatic patients

Fig. 2 *Maximum expiratory flow at 50% of vital capacity* ($\dot{V}$ *max*$_{50}$). *Lines represent the regression and ± 2 SD for the control group of children.*



(Slope = 1·97 ± 0·15, y intercept = −200·5 ± 22·1, R = 0·67).
● Nonasthmatic patients
○ Asthmatic patients

Fig. 3 *Maximum expiratory flow at 25% of vital capacity (V̇ max₂₅). Lines represent the regression and ± 2 SD for the control group of children.*

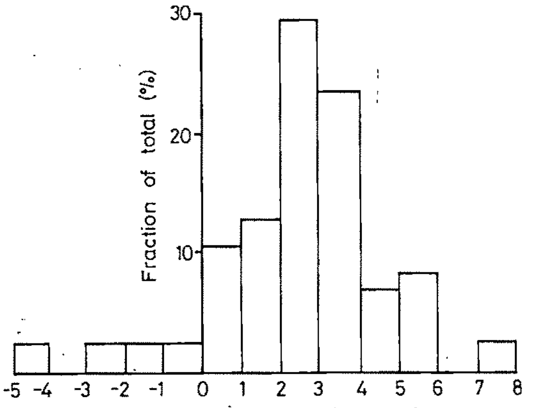


Fig. 4 *Response in flow at 50% of vital capacity after breathing a mixture of helium and oxygen (Δ V̇ max₅₀)—control group of children.*

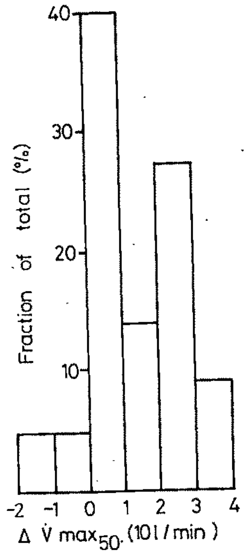


Fig. 5 *Response in flow at 50% of vital capacity after breathing a mixture of helium and oxygen (Δ V̇ max ₅₀)—study group of children excluding asthmatics.*

Table 2 *Exercise test in 34 children*

Ongoing symptoms (%)	*Fall in PEFR*		
	<10	*10–15*	*>15*
None	16	5	0
Wheeze/cough	4	1	8
Total	20	6	8

Table 2 summarises the results of the exercise study obtained in 34 patients. Of the remaining 16, 14 were preschool children who could not be persuaded to perform the test, one had a PEFR less than 70% of predicted, and another withdrew from the test after 2 minutes of exercise. 20 children showed a normal response to exercise, namely a fall in PEFR in the postexercise period of <10% of the resting value (Silverman and Anderson, 1972). The 8 children with a fall in PEFR >15% of the pre-exercise value were known asthmatics in whom a wheezing tendency antedated their mycoplasma illnesses. One of the remaining 6 children with a fall in PEFR of between 10 and 15% after exercise had only minor symptoms.

Discussion

Our results show that after clinical and radiological recovery from *M. pneumoniae* respiratory tract infection in children, routine tests of ventilatory function do not show abnormality, although the series included 10 children with wheezy bronchitis and 13 with asthma in remission at the time of study. Kjellman (1976) reported a decrease in FEV_1 and FVC in children with *M. pneumoniae* pneumonia during the acute phase of their illness, which returned to normal within a week. However, distribution of ventilation, assessed by ^{133}Xe radiospirometry, remained abnormal for a longer period and in one of 9 children persisted several months later.

Mycoplasma chest infection may be associated with wheeze in otherwise normal children, or may precipitate wheeze in those with a wheezing tendency (Berkovich *et al.*, 1970). Our series had a high proportion of children with wheezy bronchitis or asthma, including 5 patients who developed wheeze for the first time after the index illness. It seems likely that they would have developed asthma, for each had a strong background history of atopy.

The importance of exercise studies in showing increased bronchial reactivity and thus an asthmatic tendency has been demonstrated both in normal and asthmatic children (Godfrey, 1974). Our patients who had a fall in PEFR after exercise $>15\%$ of the pre-exercise value were known to have asthma and had been shown previously to have reversible airways obstruction. Sims *et al.* (1978) demonstrated bronchial hyper-reactivity in children 8 years after recovery from respiratory syncytial virus bronchiolitis in infancy, but they were careful not to infer a cause and effect relationship, but rather suggested that an environmental factor (low socioeconomic status or parental smoking) was the most likely link between respiratory infection in infancy and subsequent respiratory symptoms. Three of our 34 patients who did the exercise test gave a history of bronchiolitis in infancy from which they had recovered without further symptoms. All showed a normal response to exercise. It seems therefore that abnormal bronchial reactivity in our present series was due to including children with coexistent asthma and was not the result of antecedent bronchiolitis or the index mycoplasma respiratory illness.

It is now apparent that considerable obstruction of peripheral airways of the lung may be present before routine tests of ventilatory function show any abnormality. As a result there has been a search for new tests of lung function which are simple and sensitive (Macklem, 1972). One such test is based on a comparison of MEFV curves with the subject breathing air followed by an 80% He/20% O_2 mixture (Dosman *et al.*, 1975). We have shown an impaired response to the inhalation of this mixture at 50% of VC in a group of asymptomatic non-asthmatic children with a history of *M. pneumoniae* chest infection. It might be argued that equilibration with helium was incomplete after 3 VC manoeuvres. However, Dosman *et al.* (1975) demonstrated in symptom-free adults with normal values for routine ventilatory function tests that 3 successive VC manoeuvres were adequate to ensure equilibration with helium. This method gave results comparable with those obtained by Despas *et al.* (1972). We assumed that this was also true in our patients. The response to breathing the He/O_2 mixture was also less than in controls at 25% of vital capacity but the difference was not significant (Table 1). Impairment of response is more likely to reflect events in peripheral airways the closer to residual volume that measurements are made. However, the methodological difficulty of measuring low flow rates accurately, especially changes in flow rate, increases greatly in this part of the flow-volume curve. This may explain, at least in part, the wide range of values for $\dot{V}\ \mathrm{max}_{25}$ breathing air in both control and index cases, and account for the $\triangle\ \dot{V}\ \mathrm{max}_{25}$ being less discriminating an index of small airways dysfunction than $\triangle\ \dot{V}\ \mathrm{max}_{50}$ in the present series.

Our control data were obtained from schoolchildren attending a state primary school which served a community with children from differing socioeconomic backgrounds. Our patients were similarly drawn from varied social backgrounds. A social bias in the selection of controls is unlikely, although no attempt was made to match precisely the study and control groups of children on this basis. In our analysis of MEFV curves (Table 1) we excluded children with a background history of asthma. Thus no patient in either group had significant respiratory symptoms. We conclude therefore that impairment of response in flow rate at 50% of VC to the He/O_2 mixture was due to preceding *M. pneumoniae* respiratory infection. It is not possible to say whether the impairment of function represents permanent residual lung damage or whether these children are at risk of chronic obstructive airways disease in later life.

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Normal children with large heads—benign familial megalencephaly

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SUMMARY Fifteen normal children with large heads (circumference >0·5 cm above the 98th centile) were studied. CAT scans were performed to exclude hydrocephalus, and ventricular size was compared with that of hydrocephalic children. In 11 of the 13 families in which the parents' heads were measured, one parent (10 fathers and one mother) was found to have a large head, as had 6 of 17 siblings. Head circumference at birth was large in 7 of 10 babies and rate of head growth was excessive in 8 of 13. Skull *x*-ray showed suture diastasis in 7 infants. These families have a benign familial megalencephaly. It is important to recognise this so as to avoid unnecessary investigation and anxiety about normal children with large heads.

A large head—macrocephaly—may be due to hydrocephalus, megalencephaly, a space-occupying lesion, or a thick skull. A large brain—megalencephaly—is associated with some cerebral degenerative disorders, as well as with other conditions—for example neurofibromatosis and achondroplasia—which are usually recognised by associated physical stigmata. Isolated megalencephaly while described in some gifted individuals—for example Byron, Turgenev, Bismarck—is generally considered to be associated with fits and retardation (Laurence, 1964).

Nelson and Deutschberger (1970) related the IQ at 4 years to head circumference (HC) at one year in 9379 children. They found that those with HCs >0·5 cm above 98th centile had a slightly higher mean IQ than children with heads of average size. One family in which father and son had large heads, normal intelligence, and normal computerised axial tomography (CAT) was reported by Asch and Myers (1976). Four other normal male relatives also had large heads. DeMyer (1972) reported 18 children with large heads and normal ventricular size on pneumoencephalography (AEG), but only 5 of these were of normal stature and neurologically normal. One of these had normal relatives with large heads.

When considering whether children with large heads are normal or not it is important to exclude hydrocephalus; Laurence and Coates (1967) showed that some children with untreated hydrocephalus had average intelligence. CAT enables us to identify normal children with large heads who do not have hydrocephalus, so we studied the head growth, skull *x*-rays, CAT appearances, and head size of such children.

Method

Graphs (Nellhaus, 1968) were used to obtain standards for HC. Of 26 children who were investigated for large head size and found not to have hydrocephalus, 3 were mentally retarded and 8 had a HC only just above the 98th centile. Thus 15 children were investigated (14 CAT, 1 AEG) who fulfilled our criteria, having HCs >0·5 cm above the 98th centile and being of normal stature and developmentally and neurologically normal.

Results

Of the 15 children 11 were boys. The HC at birth was known for 10 of them and 7 were >98th centile (36·5 cm for girls, 37·5 cm for boys). Two of the children with large heads at birth were delivered with Kielland's forceps and a further child had a difficult normal delivery. The expected rate of head growth was calculated from the HC chart; in 8 children this was found to be faster than normal, 5 were growing at a normal rate, and 2 were not seen in the first 2 years of life. Four of the children had been noticed to be hypotonic in early life, one had a squint, and one speech delay.

Skull *x*-ray. All children had skull *x*-rays performed between one month and 5 years. These were examined

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independently by two radiologists. Seven of the children were thought by both, and a further 4 by one, to show suture diastasis. Cranial capacity was estimated by the method of Gordon (1966) and was >95th centile in 14 cases and on the 95th centile in one. The volume related better to the HC than to the measurements of ventricular size on CAT. One child (Case 14) had a very thick dense skull vault with a low width/length ratio and a high height/width ratio.

CAT scan appearance. 14 of the 15 children had CAT scans. The ventricular size was measured in two ways. The bifrontal and bicaudate diameters of the frontal horn of the lateral ventricle were measured at the level of the basal ganglia (as described by Hahn and Rim, 1976) and compared with brain diameter at the same site to give a ratio (cerebroventricular index). The upper limit of normal in adults for the bifrontal ratio is 39·3% and for the bicaudate ratio 23·1%.

Cerebroventricular indices in the 13 normal children with large heads are shown in Fig 1 (group A) (ventricles too small to measure in one) and compared with 8 otherwise normal children whose HC was on the 98th centile (group B), and 12 children later treated for hydrocephalus (group C). Fig. 1 shows that the indices are within the normal adult range, apart from Case 10 (Fig. 2).

As the body of the lateral ventricles is often more dilated than the frontal horns, the area of the ventricles at the level of the above measurements and at the next higher cut was measured with a planimeter and compared with the area of the brain at the respective cut to give a ratio of ventricular to brain area at two levels. These area ratios are shown in Fig. 3. The measurements of the normal large-headed children are within the same range as those with heads on the 98th centile and, with one exception, do not overlap those with hydrocephalus. This child with hydrocephalus had relatively small

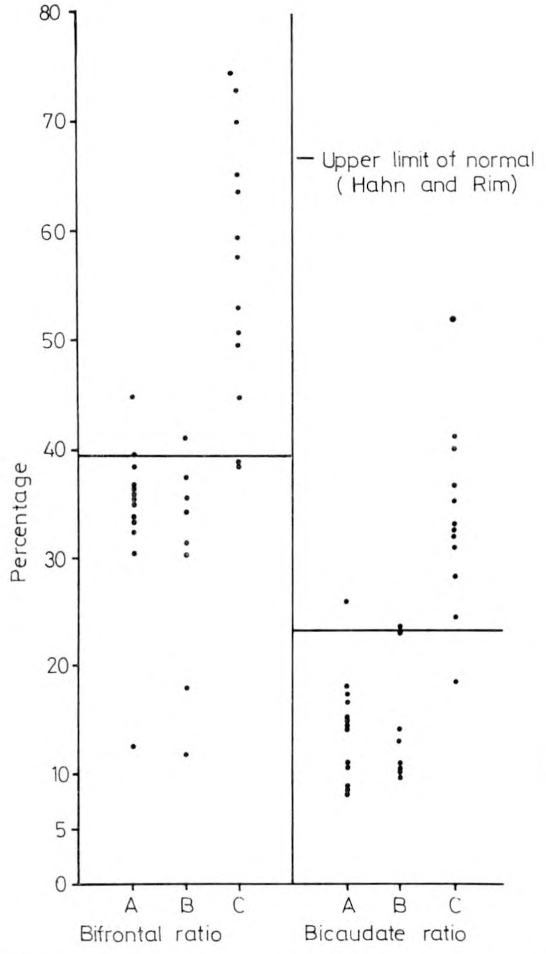

Fig. 1 *Cerebroventricular indices on CAT in (A) normal megalencephalic children; (B) normal children with HC on 98th centile; (C) hydrocephalic children.*

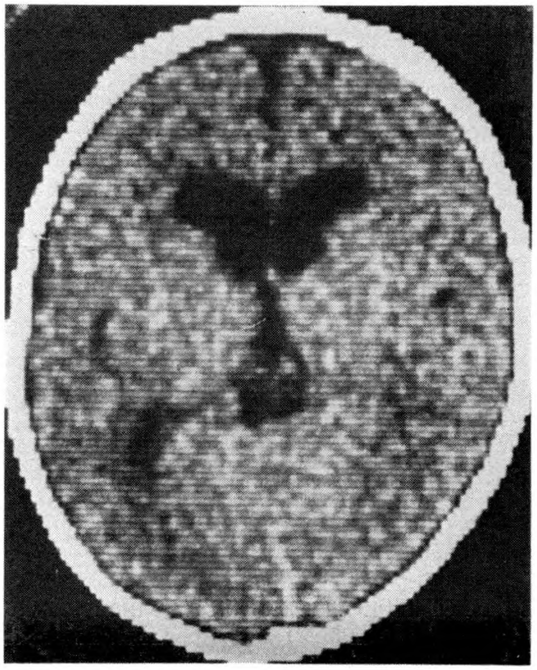

Fig. 2 *Case 10. CAT scan. Cerebroventricular indices above the upper limit of normal.*

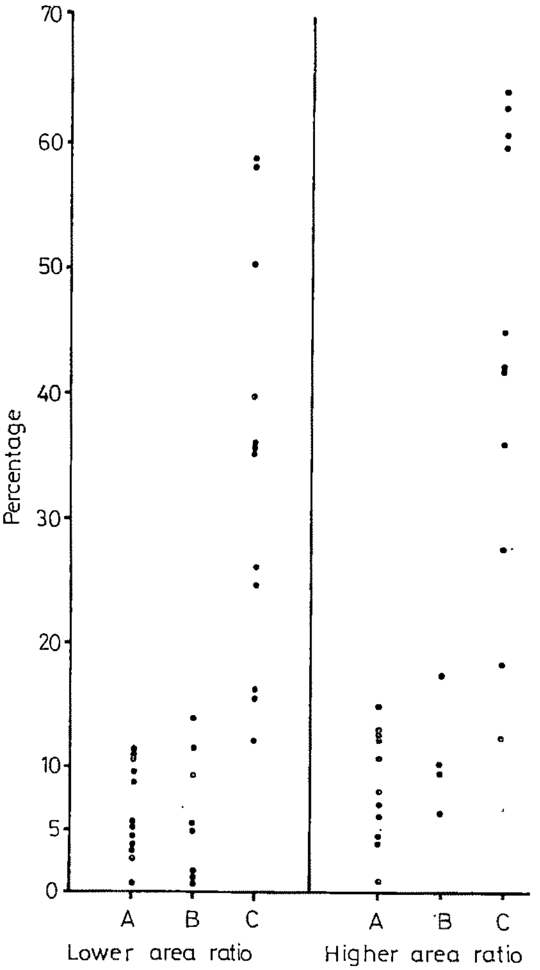

Fig. 3 *Ratio of ventricle and brain areas (A) normal megalencephalic children; (B) normal children with HC on 98th centile; (C) hydrocephalic children.*

ventricles although he had marked dilatation of the subarachnoid space and evidence of raised intracranial pressure.

Thus the normal children with large heads, except Case 10, had ventricular measurements which came within the normal range.

Family head size (Table)

Parents. Of the 15 children with large heads, 11 (10 fathers and one mother) of the parents had heads >98th centile (males >58·5 cm, females >58 cm). Only 2 children had parents with head circumferences within the normal range. Three parents were not available to be measured, one child having been adopted.

In families where the history was negative, one child (Case 13) had had viral meningitis at age 5 months and the other (Case 14) had a somewhat thick skull. The HCs of parents of 11 children in the hydrocephalus group were all <98th centile.

Siblings. Of the 11 children who each had one parent with a large head, 9 had 17 siblings (11 boys and 6 girls). Six (4 boys, 2 girls) of these had HCs >0·5 cm above the 98th centile for age. Two siblings also had hydrocephalus, of whom one had gross ventricular dilatation and was stillborn. Necropsy showed widespread old and new haemorrhage of undetermined aetiology. The other child with hydrocephalus was a twin to one of the index cases; he had a normal HC at birth which rapidly increased, and at 9 weeks AEG showed a communicating hydrocephalus which was treated with a ventriculo-atrial shunt. Of the 2 children whose parents did not have large heads, one had 2 sisters with normal sized heads and the other had a sister whose head was not measured.

Second-degree relatives. Of the 11 parents with large heads, 6 had their own parents' heads measured, and in 3 the grandfather's head and in one the grandmother's head was large. Four of the parents with large heads had siblings, in 2 the HC was normal, in one it was large, and one was not measured.

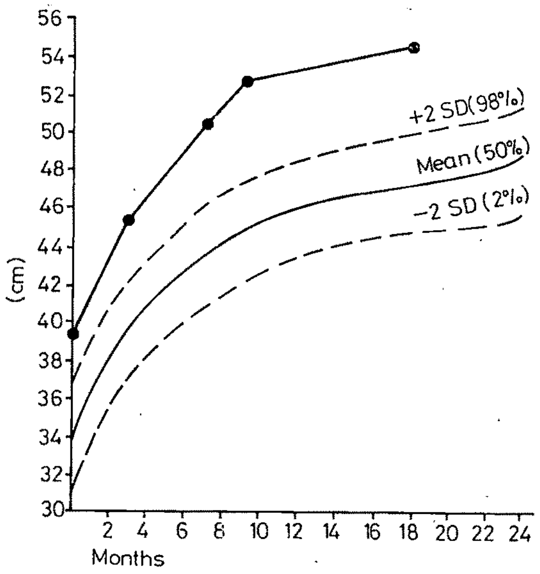

Fig. 4 *Case 6. Head circumference from birth to 18 months.*

Table *Head sizes of relatives of 15 normal children with large heads*

Case	Mother		Father		Sisters		Brothers			Grandmother		Grandfather		Siblings	
	Large (*n*=*1*)	*Normal* (*n*=*13*)	*Large* (*n*=*10*)	*Normal* (*n*=*2*)	*Large* (*n*=*2*)	*Normal* (*n*=*6*)	*Large* (*n*=*4*)	*Normal* (*n*=*5*)	*Hydro-cephalus* (*n*=*2*)	*Large* (*n*=*1*)	*Normal* (*n*=*4*)	*Large* (*n*=*3*)	*Normal* (*n*=*3*)	*Large* (*n*=*1*)	*Normal* (*n*=*2*)
1		1	1							NM		1			
2		1	1			1				NM		NM		NM	
3		1	1				1		1	NM		NM			
4		1	1				2				1	1			
5		1	1					3		NM		NM		Not known	
6		1	1				1			1			1	1	
7		1	1		1	1		1			1		1		1*
8		1	1		1			1			1		1		
9*		1	1			1			1	NM		NM			
10*		1	1								1	1			1*
11	1		NM			1				NM		NM		Not known	
12		1	NM												
13		1		1	NM										
14*		1		1		2									
15* Adopted															

NM = Not measured, *female

The following case illustrates some of these points.

Case report

A baby boy (Case 6) born at 39 weeks' gestation by Kielland's forceps for deep transverse arrest. Birthweight 4·25 kg, length 57 cm, HC 39·5 cm. He was followed up from birth and investigated at 9 months when HC was diverging (Fig. 4) and skull *x*-ray (Fig. 5) showed suture diastasis, skull volume 1390 ml (normal 925–1050). CAT scan (Fig. 6) showed bifrontal ratio 35·5, bicaudate ratio 16·6, lower ventricular area 9·0, and upper ventricular area 12·6. At 18 months the child is walking and saying several words, and development appears normal. Fig. 7 shows the family tree. Father (HC 61 cm), the elder brother (57 cm at 3 years), paternal uncle (60·2 cm), and grandmother (60·4 cm), all have large heads. The grandmother said she never seemed able to find hats to fit her.

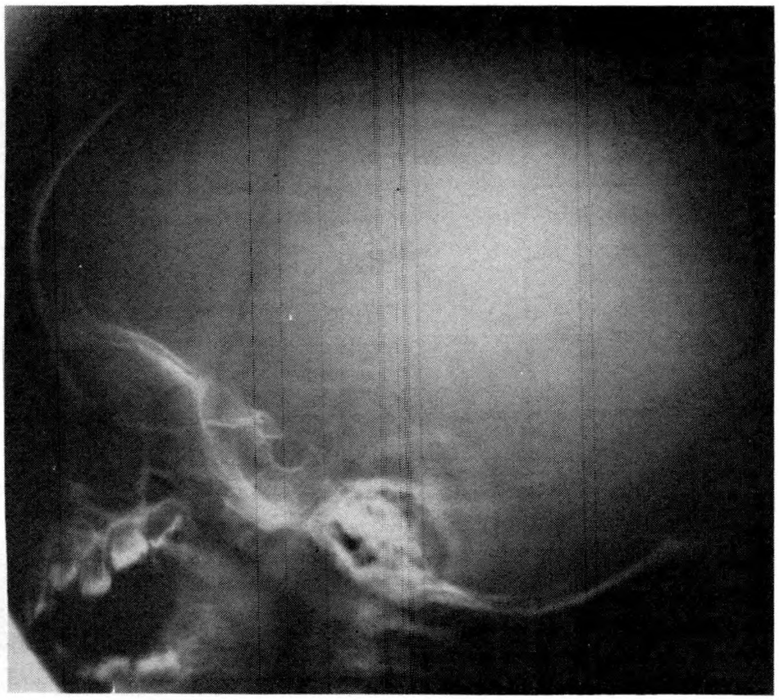

Fig. 5 *Case 6. Skull x-ray age 9 months.*

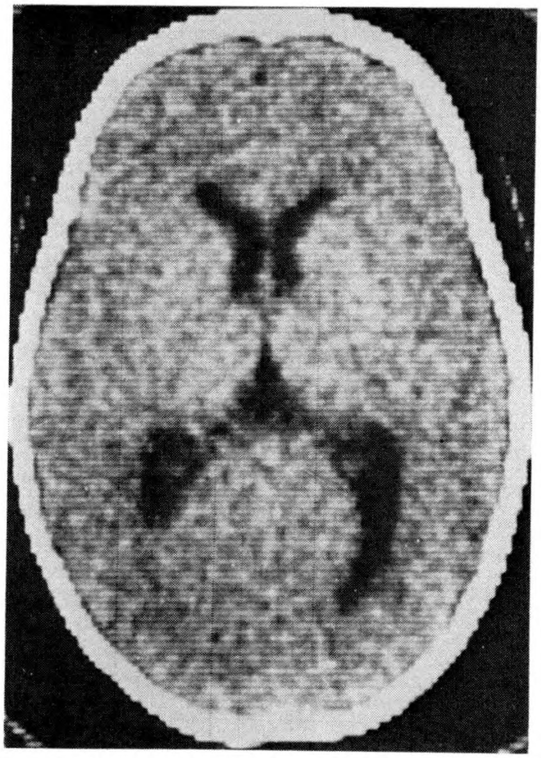

Fig. 6a *Case 6. CAT scan, cut 2A.*

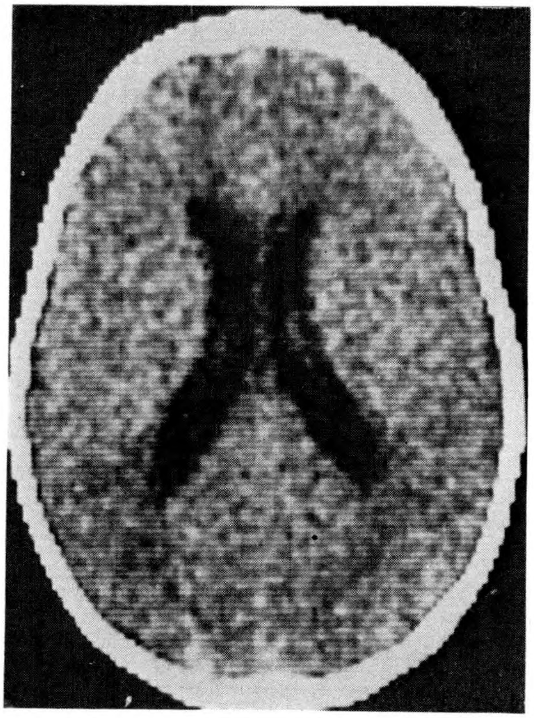

Fig. 6b *Case 6. CAT scan, cut 2B.*

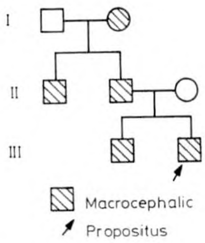

Fig. 7 *Case 6. Family tree.*

Discussion

All the 15 normal children with large heads had ventricular measurements on CAT scan which were within the normal range, except Case 10 in whom lateral ventricular measurements on low cuts (2A) were high (although well below most hydrocephalic babies). However measurement of the lateral ventricular area by planimetry was nearer the mean for the large-headed children. Nellhaus (1972) measured ventricular size by AEG and carotid angiography in 5 children with ‘benign idiopathic megalencephaly’ and found that the ventricles were in proportion with the cerebral mantle. Harwood-Nash (1977) stated that the CAT appearance of megalencephaly was that of normal or mildly dilated ventricles. Absolute measurements of ventricular size may be misleadingly high and comparison with brain size in a ratio, as done here, is more meaningful. A surprising finding in our series was of suture diastasis in 7 of the skull *x*-rays. This supports the view of Schönenberg (1973) that mild suture diastasis may not be an indication of raised intracranial pressure in young children. Conversely, he found that 12 of 39 infants with proved hydrocephalus had normal sutures.

The HC at birth was large in 7 of 10 babies. This may lead to difficulty during labour and delivery, and result in cerebral damage (Lorber and Bhat, 1974) with secondary mental retardation or neurological abnormality. Rate of head growth was increased in 8 of 13 children in whom it was measured giving the appearance of divergence from the centile lines. This was also seen in 2 of DeMyer’s (1972) tall children with large heads.

The finding that 11 of these children each had one parent with a large head and that 6 of 17 siblings also had large heads supports the suggestion of an autosomal dominant pattern of inheritance. The family described by Asch and Myers (1976) had 6 members in three generations with macrocephaly (all male). The family described by DeMyer (1972) had 4 confirmed and a further 4 suspected members with megalencephaly (4 female, 4 male) in three generations. Platt and Nash (1972) reported 4 normal children each having one parent with a large head but they did not give details. In our series there is a predominance of males 27:6 and the affected members in the family described by Asch and Myers (1976) were all males.

In two of our families one member had hydrocephalus. In one there was evidence of haemorrhage. In the other there was a communicating hydrocephalus. Schreier *et al.* (1974) described a family in which 2 members had hydrocephalus and 10 were normal with large heads. Three of these were investigated by echoencephalography which showed ventricles of normal size in one and at the upper limit of normal in two.

Thus 11 of our children have a benign familial megalencephaly which appears to be more common in males. The HC may or may not be large at birth and rate of growth may be excessive. Some of the children were hypotonic as infants but development was generally normal. Skull *x*-ray may show mild suture diastasis. CAT scan will usually clearly distinguish these children from those with hydrocephalus, although the ventricles may be at the upper limit of normal size.

It is concluded that in the absence of evidence of raised intracranial pressure or factors which might predispose to hydrocephalus or intracranial space-occupying lesion, the finding of a large head in an otherwise normal child should lead to the measurement of both parents' HC and, if one parent's head is large, the child should be observed rather than having further investigations, although CAT would reassure both doctors and parents.

We thank Dr J. L. G. Thomson and Dr I. R. S. Gordon for assistance.

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Four families with immunodeficiency and chromosome abnormalities

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SUMMARY Six children, with severe deficiency of some or all of the immunoglobulins and minor somatic abnormalities, had chromosomal abnormalities: (1) 45,XY,t(13q/18q), (2) 46,XY,21ps+, (3) two brothers 46,XY (inv. 7), (4) 45,X,t(11p/10p)/46X,iXq,t(11p/10p) and, (5) in addendum, 45,XX,−18; 46,XX, r18. The chromosome abnormalities were detected in B- as well as T-lymphocytes (as evidenced by using both PHA- and PWM-stimulated cultures) in all probands, but one was mosaic in PHA culture, although all his PWM-stimulated cells were abnormal. Chromosomal variants were also detected in relatives of three and immunodeficiency in relatives of two.

Only two firm associations between immunodeficiency and autosomal chromosome abnormality in phytohaemagglutinin (PHA) stimulated T-lymphocytes are recognised. Some patients with ataxia telangiectasia show general chromosome instability with many spontaneous breaks (especially of chromosome 14 and other D-group chromosomes) (Nelson *et al.*, 1975; Oxford *et al.*, 1975). IgA deficiency is sometimes associated with chromosome 18 abnormalities—deletions of short and long arm (Feingold *et al.*, 1969; Faed *et al.*, 1972), ring forms (Finley *et al.*, 1968), and large chromosomes (Yanagisawa, 1972). There are also reports of immunodeficient patients with other chromosomal abnormalities (Jacobs *et al.*, 1968; Kretschmer *et al.*, 1968; Calvani *et al.*, 1976), especially of the D-group. We studied the chromosomes in four immunodeficient children who had unusual facies; each had an abnormality.

As the immunodeficiency was of antibody we studied the chromosomes not only in PHA-stimulated lymphocytes (predominantly T-lymphocytes), but also in pokeweed mitogen- (PWM) stimulated lymphocytes (which include B-lymphocytes).

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Methods

Immunoglobulins were measured by radial diffusion (Fahey and McKelvey, 1965). Lymphocyte thymidine uptake after PHA stimulus, E-rosette count, and surface immunofluorescence were by the method of Espanol *et al.* (1974). Chromosomal analysis of PHA-stimulated lymphocytes after colcemid treatment was by the method of Hungerford (1965).

For chromosomal analysis 0·05 ml PWM (Gibco, New York) was added to 5 ml cultures (Wybran *et al.*, 1973).

T- and B-enriched preparations of lymphocytes were prepared by rosetting techniques from Case 1 and a healthy donor, cocultured with PWM, and tested for cytoplasmic immunofluorescence for immunoglobulin (Hayward and Lawton, 1977).

Buccal smears for X-chromatin studies were prepared by a modification of the method of Klinger and Ludwig (1957). Hydrolysis in 1 mol/l HCL for 8 minutes was followed by staining for 10 minutes in 2% aqueous toluidine blue.

Family 1. Case 1, a boy, was investigated soon after birth because his maternal uncle had had life-long immunoglobulin deficiency (he died before the proband's birth). At birth Case 1 had limb swelling, deformed toe nails, spindle shaped fingers, microcephaly, and an unusual facies with fullness over the maxillary and mandibular bones. Immunoglobulin deficiency was found (see below) and replacement treatment was started, although he had had no obvious infection. At 15 months he developed convulsions, up to five a day. Several members of his father's family had had convulsions. Neutropenia was noted once. Levels of serum IgG, IgA, and IgM have been persistently very low. Lymphocyte count was normal with normal E-rosette count, and a high percentage positive for surface immunoglobulin immunofluorescence (Table). Chromosome analysis of PHA-stimulated cells showed a normal/translocation mosaic; 3 of 10 cells studied were normal;

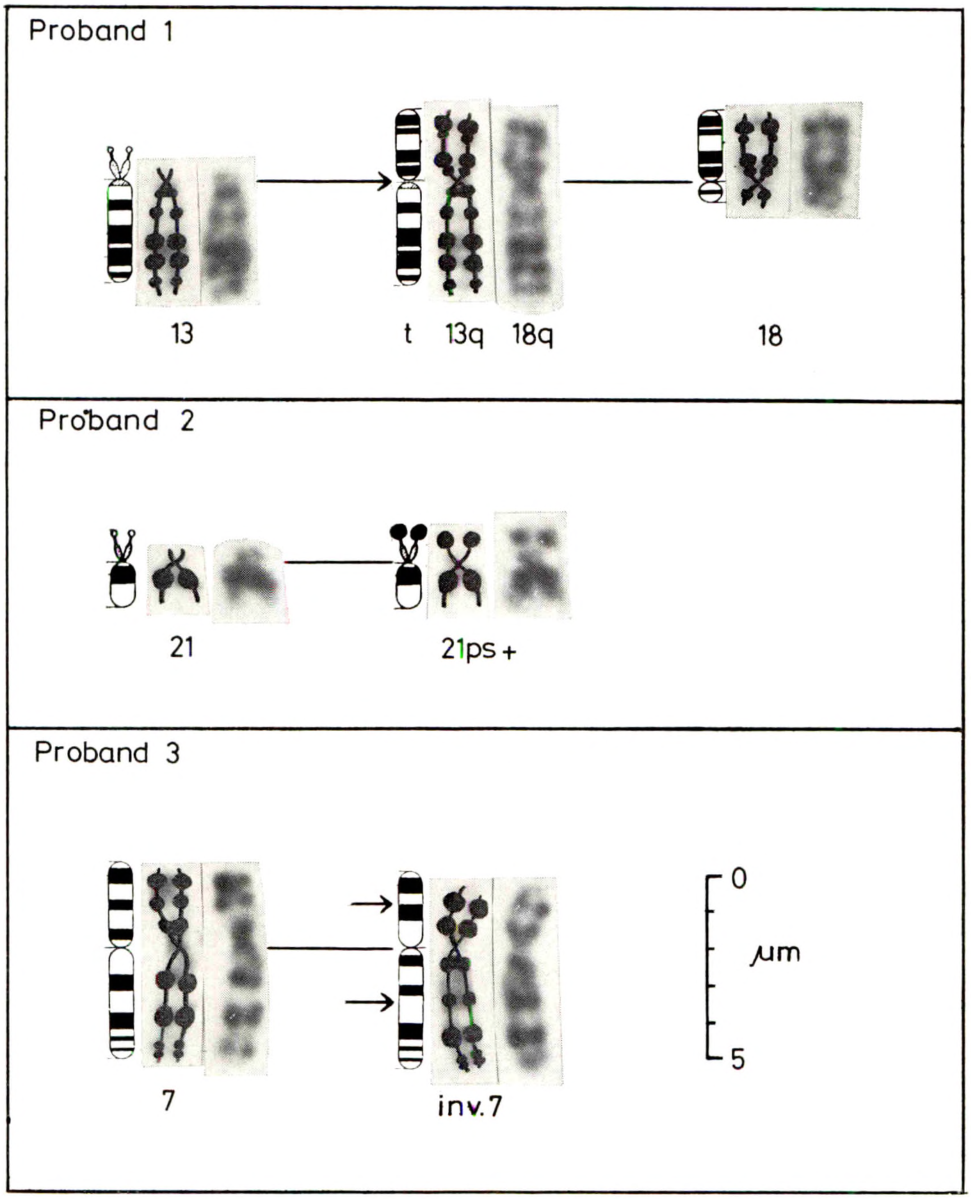

Fig. 1 (scale in microns). *Anomalous chromosome pairs from probands 1, 2, and 3. Photomicrographs of the normal and abnormal member of each affected chromosome pair are shown, in each patient, together with a drawing and the standard international diagram of the banding pattern (Paris Conference, 1972). Translocated chromosome in proband 1 (a mosaic) was formed by fusion of chromosomes 13 and 18, after loss of their short arms by breakage at the centromere (arrowed). Proband 2 has large satellites on chromosome 21. In proband 3, the arrows pointing to the inverted chromosome 7 (inv. 7) indicate the apparent breakage points at which the order of the bands has been reversed.*

Table *Immunological data on patients with immunoglobulin deficiency and chromosomal abnormalities. Lymphocyte PHA response is expressed in maximum DPM/0·01 ml whole blood. Lymphocyte forming rosettes with sheep red cells (E–RFC) and with surface immunoglobulin (SIg^+) are expressed as %*

Family	*Subject*	*Age*	*Neutrophils* (× 10^9/l)	*PHA response*	*Lymphocyte %*		*Serum (IU/ml)*		
					E-RFC	*SIg^+*	*IgG*	*IgA*	*IgM*
1	Proband	7/12	0·11 → 2·63	13,923	57	34	28	<3	<3
	Mother	Adult	5·70	6,979	59		94	123	193
	Father	Adult	2·86	13,915	7		141	135	193
2	Proband	9/12	3·24	23,006	58	14	38	<3	26
	Sibling	4 years	6·08	22,454	66	14	70	40	72
	Mother	Adult	8·86	14,914			120	84	192
	Father	Adult	7·08	3,162	71		118	151	86
3	Proband	4/12	0·74–6·03	29,290	56	15	26	3	43 → 104
	Sibling	3 years	0·77	3,861			6	24	>170
	Mother	Adult	3·30	2,057			128	132	312
	Father	Adult	3·42	5,945			136	88	208
4	Proband	3/12	6·14	4,135	60	14	28	9	106
	Mother	Adult	5·23	2,478	65	11	171	59	261
	Father	Adult					174	149	128

in the remainder the long arm of an 18 was translocated on to the long arm of a 13; both the short arms were missing (Fig. 1). In PWM-stimulated cultures all 30 cells studied showed the translocation.

T- and B-enriched preparations from Case 1 and a healthy donor were co-cultured in different combinations and, after PWM stimulus, tested for cytoplasmic immunofluorescence for immunoglobulin; donor B-cells were positive whether cultured with autologous T-cells (6·5 × 10^4/well) or T-cells from proband 1 (9·3 × 10^4/well) but no positive cells were seen (<0·05 × 10^4/well) when B-cells from the Case 1 were cultured with either autologous or female donor T-cells.

His father had normal chromosomes in all PHA-stimulated cells, but count of E-rosette-forming cells was low (one study only, Table, Fig. 2). The immunological tests on his mother were normal, but the one cytogenetic study made suggests that she is mosaic, as 2 of 20 cells had an extra C-group chromosome. The uncle had had IgG and IgA deficiency with normal levels of serum IgM; no lymphocyte or chromosome studies were done.

Follow-up of Case 1 had shown retarded intellectual development, but convulsions have become less frequent without prophylactic treatment, and he has had no infections while on immunoglobulin injection.

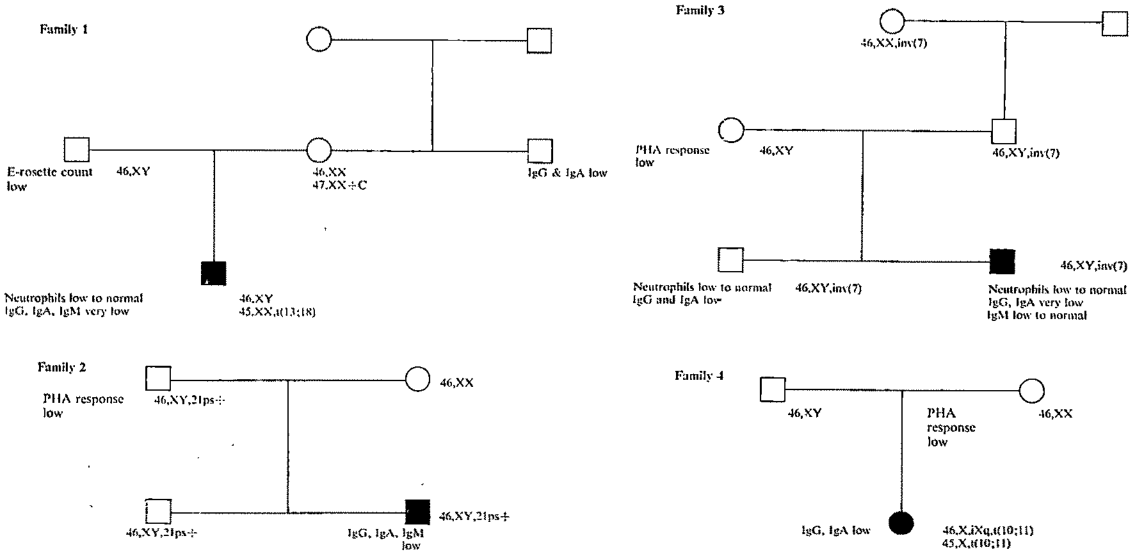

Fig. 2 *Family trees of 4 probands (● ■) with abnormalities of chromosomes and immunoglobulins. Abnormal immunological findings and results of chromosome analysis of PHA-stimulated lymphocyte cultures are given.*

Family 2. Case 2, a 9-month-old boy, was investigated for growth retardation, developmental delay, and repeated febrile illnesses with convulsions. He had an unusual facies, with a mongoloid slant to the eyes, hypertelorism, anteverted nares, and broad upper lip. He had hyperextensible joints and pigmented naevi on the occiput, thigh, and axilla. A cystogram showed bilateral ureteric reflux with parenchymal opacification of the left kidney. His head was asymmetric and a CAT scan showed cortical thinning, especially of the frontal lobes. There was evidence of respiratory and urinary infections.

Levels of serum IgG, IgA, and IgM were all very low. Salivary IgA and isohaemagglutinins were absent. Chromosome analysis of both PHA- and PWM-stimulated lymphocytes showed that all cells had a giant satellite on the short arm of chromosome 21 (Fig. 1). He has since had occasional mild respiratory infections while on prophylactic co-trimoxazole, and his convulsions are well controlled on sodium valproate; his psychomotor development is retarded.

His mother's immunological tests were normal, as were her chromosomes. Both his father and 4-year-old brother were well, but show the same chromosome aberration in all PHA- and PWM-stimulated cells. Although the brother is immunologically normal, his father has a low PHA response (Table).

Family 3. Case 3, a 4-month-old boy, was investigated for growth retardation and feeding difficulties. He had an unusual facies, with a low set left ear, anti-mongoloid slant to the eyes, and high arched palate. He was wasted and breathless. *Pneumocystis carinii* infection was diagnosed on lung aspiration and *Giardia lamblia* were found in the faeces. He had intermittent neutropenia and low levels of IgG and IgA. IgM was low but rose to normal. The anti-A isoagglutinin titre was 1/1. Salivary IgA was not detected. There was pericentric inversion of chromosome 7 on all cells on PHA and PWM cultures (this had previously been identified in PHA culture by Dr N. Gregson). He gained weight after treatment with immunoglobulin injections, co-trimoxazole, and metronidazole.

His mother had a low PHA response, but her other immunological tests and her chromosomes were normal. His paternal grandmother, father, and 4-year-old brother each showed the same chromosome abnormality. His father was well and immunologically normal. His brother had neutropenia on one occasion and has low levels of serum IgG and IgA. He was relatively well until recently apart from mild oral ulceration; this is now severe and immunoglobulin treatment has been started.

Family 4. Case 4, a 3-month-old girl, was investigated for growth retardation, prolonged hypocalcaemia (until 9 weeks old), and frequent infections: chronic oral and perineal candidiasis, chronic paronychia and pulp space infection, and septic arthritis of the hip. She had an unusual facies with micrognathia, high arched palate, and epicanthic folds. Pectus excavatum, widely spaced nipples, stridor, large umbilical hernia, hypotonia, anterior bowing of tibiae, and dystrophic nails were noted. Barium meal showed malrotation of the intestine.

Serum IgG and IgA were low and salivary IgA was not detected. E-rosette-forming cells, PHA response, and surface immunoglobulin immunofluorescence were normal. Of 20 cells studied, on PHA stimulus, 9 had a single X-chromosome (45, X) and 11 had an isochromosome for the long arms of X—that is she was a mosaic (Fig. 3). All lymphocytes showed an extra band on the short arm of chromosome 10, and a missing band from the short arm of chromosome 11. PHA and PWM cultures gave similar results. Of 300 buccal cells 16% showed Barr bodies (normal female range 15 to 30%); some were abnormally large. Her parent's chromosomes were normal; the mother's PHA response was low.

She has had no subsequent serious infections and serum calcium has remained normal without further treatment, but there is evidence of psychomotor retardation.

Discussion

The association of immunoglobulin deficiency with chromosome aberrations and abnormalities raises a number of possibilities. It may be coincidental as autosomal abnormalities are found in about 0·3% of newborn babies (Evans, 1977), and we are becoming increasingly aware that immunodeficiency is not rare. The occurrence of both in a single individual will be an occasional chance finding, but the detection by chance of a significant chromosomal abnormality or variation in all four probands we studied would be a very odd run of luck. It is possible that the structural and chromosomal abnormalities were causatively associated, and immunodeficiency, which brought them to our attention, was associated by chance.

The other possibilities for the association are that the chromosome abnormality may cause the immunodeficiency, or that the immunodeficiency may have led to abnormal handling of an intra- or extra-uterine viral infection by the child or the mother which might have caused the chromosome abnormality, or that both were caused by the same environmental factor, for instance by a virus infection (Soothill *et al.*, 1966). There is no history

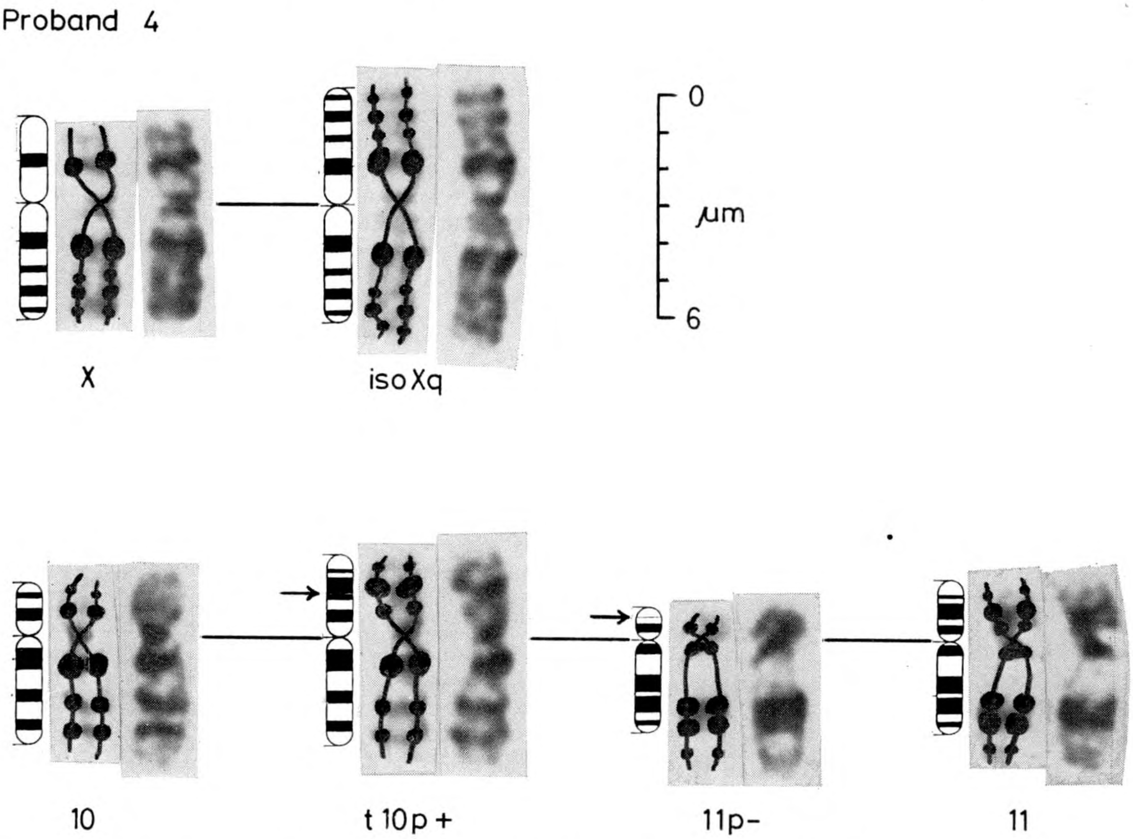

Fig. 3 (scale in microns). *Anomalous chromosome pairs from proband 4, presented in the same way as in Fig. 1. In addition to the normal X and isoXq (with its duplicated long arm), there are two abnormal autosomes which seem to be balanced for a translocation between chromosomes 10 and 11. Arrows indicate the apparent breakage points at which part of the short arm of an 11 broke off to become attached to the short arm of a 10.*

of overt viral infection during pregnancy in any of these families. It is very likely that the mechanism of the associations may be different in the different families. In families 2 and 3 it is more likely that they were coincidental as the chromosome abnormality was detected in an immunologically and structurally normal member of both families, but one cannot exclude the possibility that the abnormalities resulted from varying expression of the chromosome defect. The neutropenia in association with inversion of chromosome 7 in Case 3 is interesting in view of the report by Rowley (1973) of neutropenia with deletions of this chromosome. The known involvement of X-chromosome with immunoglobulin concentration (Butterworth *et al.*, 1967; Rhodes *et al.*, 1969) gives added significance to the finding in Case 4.

Although the family tree (Fig. 2) in family 1 suggests X-linkage, neither the normal IgM in the uncle, nor the normal number of lymphocytes with surface immunoglobulin in the child is consistent with X-linked agammaglobulinaemia, but there probably are other forms of X-linked immunodeficiency. Coincidental chromosomal abnormality with such an immunodeficiency must be considered, but there is evidence in favour of a causative relationship. The mosaicism of the T-lymphocytes (with apparently normal T-cell function, including that of co-operation) but the consistent chromosomal abnormality in the PWM-stimulated cultures, many of which would be B-lymphocytes which were functionally defective *in vitro* and *in vivo* would be an additional coincidence if the relationship were not causal.

The chromosomes affected in Case 1 have been previously associated with immunodeficiency—chromosome 18 with IgA deficiency (Feingold *et al.*, 1969; Faed *et al.*, 1972), and group- D chromosomes with IgM deficiency (Kretschmer *et al.*, 1968), and severe combined immunodeficiency (Calvani *et al.*, 1976). An association between swollen feet and chromosome 18 abnormality has been described (Vianna-Morgante *et al.*, 1976) without immunological data. Perhaps there was a generalised genetic predisposition to chromosome instability involving the C-group defect in the mother, the 13/18 in the child, and one which we can only guess at in the uncle, causing the immunodeficiency.

Cytogenetic study of both PHA- and PWM-stimulated cultures permits study of variation of mosaicism in different cell populations and organ-specific cell selection. Full interpretation of these relationships demands more data, but if such associations are found consistently, they may throw light on the chromosome distribution of genes which control immunity mechanisms, other than those already described.

Addendum

Since completing this paper we have observed a child with a ring 18-chromosome, who showed the somatic abnormalities and IgA deficiency similar to the child described by Finley *et al.* (1968). Our patient was mosaic for this abnormality (3 cells 45, XX, −18; 17 cells 46, XX, r 18).

We are grateful to Dr N. Gregson who first observed the chromosomal abnormalities in family 3, to Dr J. Stewart for help with studies on family 4, to Professor O. Wolff and Dr J. T. Harries under whose care the probands were admitted, and to Miss Doreen M. Farrington and Mrs Janette D. O'Connell for technical help.

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Effects of physical training on hormonal responses to exercise in asthmatic children

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SUMMARY A 4-month period of physical training increased the physical working capacity of 16 asthmatic children (aged between 9·3 and 13·6 years) by a mean of 11%. The increase was greater in boys and was negatively correlated with pretraining capacity. Urinary excretion of adrenaline, measured during a submaximal exercise test, decreased during the training period; the decrease was correlated with the increase in working capacity. Before the training period, exercise induced an increase in the plasma cortisol level; no increase was evident after training. In contrast, the training did not affect the exercise-induced increase in the plasma growth hormone level.

Training programmes have been evaluated (Geubelle *et al.*, 1971; Vavra *et al.*, 1971; Fitch *et al.*, 1976) for improving the poor physical fitness of asthmatic children (Fowler and Gardner, 1963; Godfrey, 1974). The disturbing effect of exercise-induced bronchospasm (Jones *et al.*, 1962; Bierman *et al.*, 1975) can be avoided by swimming training (Fitch *et al.*, 1976) or by dividing the training into short bursts of activity (Strick, 1969). Exercise stimulates the secretion of several hormones (Felig and Wahren, 1975) and training may modify the responses (Hartley *et al.*, 1972a). Therefore, we set out to study whether the exercise-induced responses of adrenaline, cortisol, and growth hormone (GH) would change during a training programme for asthmatic children.

Subjects

Eight boys and 8 girls (see Table for clinical data) consented (with the approval of their parents) to participate in the exercise tests and the training programme. All the children had bronchial asthma diagnosed more than 4 years earlier. Five children had a history of exercise-induced asthma; all of them, and 2 others, used sodium chromoglycate inhalations. No oral corticosteroids were used, but 2 children took daily inhalations of beclomethasone. Sympathomimetic medication, if any, was stopped at least 10 days before the tests. No healthy child participated in the programme.

Training programme

During 4 winter months the children were offered a total of 31 sessions of training, on Mondays and Thursdays, after school in a gymnasium under the supervision of a physiotherapist. The children used a mean of 19 sessions, with a range of 12 to 28. The 60-min training session consisted of 10 min of warming up with light gymnastics, 5 min of breathing exercises, a 20-min period of four 1-min bursts of maximal activity (skipping-rope, fast jumping, stepping chair exercises, etc.), interrupted by rest and/or light gymnastics, 5 min of light exercises (rings, parallel bars, etc.), and 20 min of ball games or other sports (football, table tennis, relay race, etc.). In the rare case of exercise-induced bronchospasm the child took a break and did light breathing exercises until the attack ceased. No sympathomimetic drugs were needed.

Methods

The children were tested within 2 weeks before the beginning (pretraining test) and within 2 weeks after the end (post-training test) of the training programme. In the morning an indwelling venous cathether was introduced for collecting blood samples. Just before the test, the child urinated and a basal blood sample

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was taken. Then samples were taken half-hourly for 2 hours, a 2-hour urine sample was collected, and tetracosactide (S-Cortrophin, Organon, Netherlands), 0·15 mg/m^2, was given IV for a 2-hour ACTH test (Leisti and Perheentupa, 1978a). Blood samples were taken without stasis into heparinised Pyrex tubes, which were placed immediately in an ice-water bath. Plasma was separated after the last sample. Urine was collected in glass containers, which included 5 ml HCl, 6 mol/l. Both plasma and urine samples were stored in a freezer. All samples from the same child were assayed in the same run at the end of the programme.

Submaximal bicycle ergometer tests were modified slightly from the scheme proposed by Sjöstrand (1967). The three 4-min loads were chosen individually in order to achieve the pulse rates of 80–90, 100–120, and 150–160 beats/min, respectively. In the postexercise tests the same loads were used. Then the physical working capacity for the pulse rate 180 beats/min was determined graphically. The result was expressed in watts per m^2 of surface area (1 W = 6·12 kpm/min). We prefer correction by surface area to correction by weight or by height, because, according to our calculations made on the data of Adams *et al.* (1961), the effects of age and sex are both best corrected by this method in this age group.

Peak expiratory flow rate (PEFR) (Kattan *et al.*, 1978) was determined immediately before the exercise test, and again 8–10 min after the end of the test. The highest value achieved in three attempts was used for calculation of the percentage change from the pre-exercise value. Plasma cortisol was determined with a fluorometric method (Leisti and Perheentupa, 1978a), plasma GH with a radioimmunoassay (Leisti and Perheentupa, 1978b), and urinary adrenaline with a fluorometric method (Crout, 1961). Student's 2-tailed *t* test (for differences between boys and girls), Student's paired *t* test (for differences between pre- and post-training values), and correlation coefficients were used for evaluating the results.

Results

Effect of training on working capacity. Working capacity was increased by a mean of 11% (15% in the boys, 10% in the girls; see Table). The increase was not correlated with the total number of participations in the training programme (r = −0·16), but was clearly negatively correlated with the pretraining working capacity (r = − 0·54, $P<0{\cdot}05$).

Effect of training on exercise-induced change in PEFR. A decrease of more than 15% was seen in two children during the pretraining test, and in one more child in the post-training test. Training had no clear effect on the submaximal exercise-induced change in PEFR, and the individual patterns seemed to remain consistent (Table).

Effect of training on exercise-induced hormonal response. The mean urinary adrenaline response decreased by 46% during the training period (Table). The effect was clearer in boys (55%) than in girls (29%); girls also had lower mean responses in both pre- and post-training tests. The decrease in adrenaline response correlated significantly with the increase in working capacity (Fig. 1).

Exercise induced an increase in the mean plasma cortisol level in the pretraining test, but this was no longer evident in the post-training test (Fig. 2). However, maximum cortisol levels were not significantly lower in the postexercise tests. Boys had higher maximum cortisol levels in the pretraining tests than girls, but after training there was no difference. Training had no effect on the ACTH test response (Table).

Exercise induced an increase in the mean plasma GH level in both tests (Fig. 2). Training had no effect on the GH response.

No correlations were detected between the pretraining working capacity and pretraining hormonal responses, or between the same variables measured after the training period. The plasma lactate response was not altered by the training, but boys had higher mean values in the pretraining test than girls (Table).

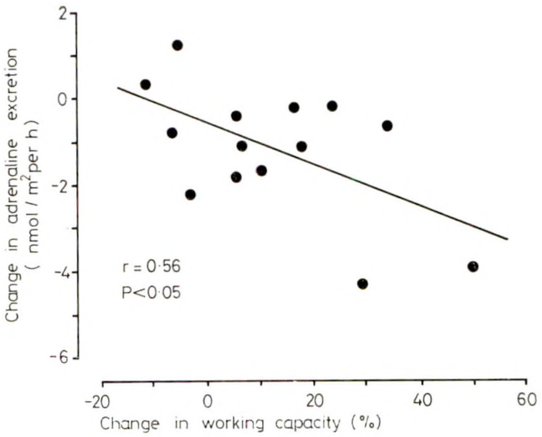

Fig. 1 *Change in the working capacity related to change in urinary adrenaline excretion during a 4-month course of physical training in 14 children with bronchial asthma.*
Conversion: SI to traditional units—adrenaline: 1nmol ≈ 0·18 μg.

Table *Clinical data and responses of 16 asthmatic children to submaximal bicycle ergometer test before and after a 4-month training period*

Case	*Age (years)*	*Continuing treatment*	*Exercise-induced variables*												*ACTH test*	
			Working capacity (W/m²)		*Change in PEFR (%)*		*Maximum plasma lactate (mmol/l)*		*Urinary adrenaline 2-h excretion nmol/(m² per h)*		*Maximum plasma GH (μU/l)*		*Maximum plasma cortisol (nmol/l)*		*Plasma cortisol 2-h level (nmol/l)*	
			Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
Boys																
1	13·6	SC, BI	110	103	0	4	2·2	2·3	2·7	1·9	42	24	770	300	990	900
2	13·4	—	54	58	3	−1	2·3	2·2	2·9	1·8	12	16	660	570	1460	1260
3	12·6	—	56	72	−8	−8	1·7	1·8	5·8	1·5	<1	<1	980	510	1560	1380
4	11·3	SC	79	77	7	−2	2·4	2·8	4·5	2·3	4	21	470	230	1060	920
5	10·8	SC	66	81	7	30	1·7	2·5	—	—	40	22	470	650	910	880
6	10·2	SC	48	72	−4	−51	1·8	2·0	5·6	1·7	61	16	950	1270	950	1350
7	9·6	—	78	91	−4	−7	2·1	2·1	1·0	1·2	23	7	280	360	800	790
8	9·3	—	54	66	−16	−28	2·8	2·2	—	—	28	15	650	260	1090	1060
Mean			68	78	−2	−8	2·1	2·2	3·8	1·7	27	15	650	520	1100	1070
SEM			7	14	3	8	0·1	0·1	0·8	0·7	7	3	90	120	90	80
P for the difference			<0·05		NS		NS		<0·05		NS		NS		NS	
Girls																
9	13·1	—	64	61	−8	1	1·8	1·9	0·1	1·3	39	25	360	460	1450	1260
10	12·2	BI	49	61	6	0	2·1	1·9	1·1	0·9	3	9	400	440	1000	1140
11	12·2	—	72	64	5	−1	2·2	2·0	1·1	1·4	47	67	250	430	940	1020
12	11·6	—	64	86	6	4	1·6	2·7	2·0	1·3	<1	<1	480	360	1270	990
13	11·3	SC	60	63	−18	−15	2·0	2·6	3·1	1·3	1	23	220	300	1030	1020
14	10·4	—	70	78	3	1	1·3	1·6	2·9	1·2	17	17	340	340	1130	980
15	10·2	SC	51	55	0	−7	1·5	2·0	1·1	0·7	27	<1	410	300	1460	1300
16	10·1	SC	45	53	10	−9	1·3	1·7	2·4	1·3	25	11	740	540	1240	1270
Mean			59	65	0	−3	1·7	2·0	1·7	1·2	20	19	400	400	1190	1120
SEM			4	4	9	2	0·1	0·1	0·4	0·1	6	8	60	30	70	50
P for the difference			NS		NS		NS		NS		NS		NS		NS	
All children																
Mean			64	71	−1	−6	1·9	2·1	2·6	1·4	23	17	530	460	1150	1090
SEM			4	3	2	4	0·1	0·1	0·5	0·1	5	4	60	60	60	50
P for the difference			<0·01		NS		NS		<0·02		NS		NS		NS	
P for the difference between boys and girls			NS	NS	NS	NS	<0·05	NS	<0·05	<0·01	NS	NS	<0·05	NS	NS	NS

SC=Sodium chromoglycate, BI=inhaled beclomethasone, NS=not significant.
Conversion: SI to traditional units—power: 1 W ≈6·12 kpm/min, lactate: 1 mmol/l ≈9 mg/100 ml, adrenaline: 1 nmol ≈0·18 μg, cortisol: 1 nmol/l ≈0·036 μg/100 ml.

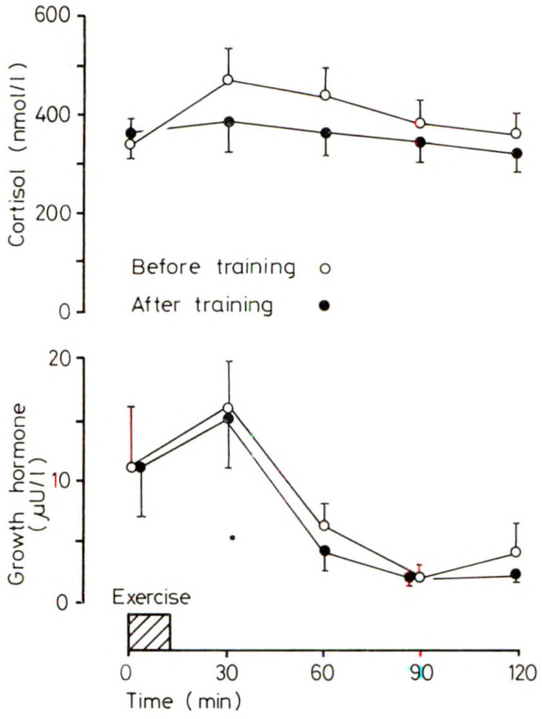

Fig. 2 *Exercise-induced mean levels of plasma cortisol and GH in 16 children with bronchial asthma; effect of 4 months' physical training on the response.*
Bars indicate SEM.
Conversion: SI to traditional units—cortisol: 1 nmol/l ≈ 0·036 μg/100 ml.

Discussion

Our 4-month biweekly training programme increased the physical working capacity and decreased submaximal exercise-induced responses in urinary adrenaline excretion and plasma cortisol levels in a group of asthmatic children. In contrast, GH response was not affected by the training.

As no healthy child was included, no direct comparisons can be made of the efficiency of our programme. However, the mean increase of 11% above the pretraining capacity for physical work is comparable with the increase of 15% in 6 healthy boys during a 6-month course of intensive training (Ekblom, 1969) and with the mean increase of 11% in 46 asthmatic children during a course of 5 months of swimming training (Fitch *et al.*, 1976). In most asthmatic children a 4- to 6-min period of hard exercise triggers an attack of bronchospasm (Jones *et al.*, 1962; Bierman *et al.*, 1975) with deleterious effect on the training intensity. Failure to compensate for this effect may explain the failure of some intensive training programmes (Geubelle *et al.*, 1971; Vavra *et al.*, 1971). We avoided this effect by dividing the intensive training into short bursts of activity (Strick, 1969). In accord with Fitch *et al.* (1976), training did not affect the frequency of submaximal exercise-induced bronchospasm.

Exercise-induced increases in the secretion of adrenaline (Galbo *et al.*, 1975), cortisol (Few, 1974), and GH (Sutton and Lazarus, 1976) are directly proportional to the intensity of the work. Because the loads between the two tests were unchanged in our series, our findings could be explained by assuming that the ratio of work load to physical working capacity was decreased during the training period. Unchanged plasma lactate levels indicate that the decrease in this ratio was not crucial.

In trained healthy adults, submaximal exercise (Hartley *et al.*, 1972a) or prolonged exercise before exhaustion (Hartley *et al.*, 1972b) induced a lower response in plasma adrenaline level after a 7-week period of training. However, at maximal loads or after exhaustion the responses were unchanged. Plasma cortisol and GH levels indicated no consistent changes. Basal urinary adrenaline or urinary cortisol excretion showed no changes during a period of 6 weeks' training in healthy or obese adult men (Björntorp *et al.*, 1977). In untrained asthmatic children maximum exercise induced an increase in plasma adrenaline level similar to that seen in healthy children (Chryssanthopoulos *et al.*, 1978). Our results are inferred from short submaximal exercise tests and therefore cannot be generalised. Training could induce changes in exercise responses by modifying the rate of secretion, peripheral degradation or excretion of the hormones (Few, 1974), or the rate of blood flow in the adrenal glands.

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Dubin-Johnson syndrome with some unusual features in a Chinese family

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SUMMARY Three cases of chronic nonhaemolytic jaundice with conjugated bilirubin in the serum are described in a Chinese family. Bromsulphthalein excretion tests gave results typical of the Dubin-Johnson syndrome. Liver histology in the proband showed cytoplasmic pigment of the lipofuscin-melanin variety, and intravenous cholecystography failed to show visualisation of the gallbladder. Unusual findings included onset during the neonatal period in the proband and the presence of some iron pigment in the hepatic cells with a little canalicular cholestasis. It is suggested that the infant may have had a concomitant nonspecific hepatitis. These cases are regarded as belonging to a disease group in which the Dubin-Johnson syndrome is at one end of a spectrum. The mode of inheritance is discussed.

The hereditary defects in bilirubin metabolism are rare and incompletely understood causes of jaundice. They can be divided into two groups according to whether the raised serum bilirubin level occurs only in the unconjugated form as in Gilbert's disease (Berk *et al.*, 1970) and Crigler-Najjar disease (Crigler and Najjar, 1952), or in both the conjugated and unconjugated forms. The best known of the latter group was first described by Dubin and Johnson (1954) and independently by Sprinz and Nelson (1954). It is characterised by the accumulation of an unidentified pigment in the liver cells which is probably composed of melanin precursors which polymerise and are stored in lysosomes, although it is often called lipofuscin by pathologists (Arias, 1971). A closely similar clinical and biochemical disorder but without abnormal pigment in the liver cells was first described by Rotor *et al.*, 1948. In this paper we describe three cases of chronic nonhaemolytic jaundice with conjugated bilirubin in the serum in a Chinese family.

The proband

A Chinese male infant, the 4th child of healthy unrelated parents, was born spontaneously in the United Christian Hospital, Hong Kong on 22 March 1978. The birthweight was 3·58 kg. There was no history of maternal illness, drug ingestion, or x-irradiation. Jaundice was noted on day 2 when the total serum bilirubin (SB) level was 225·7 μmol/l (13·2 mg/100 ml). This rose to 299·3 μmol/l (17·5 mg/100 ml) on day 3 when phenobarbitone and phototherapy were started. Hb was 13 g/dl. G-6-PD deficiency was excluded. The mother's blood group was A Rh +ve, the infant's AB Rh +ve. The infant continued to feed well on a proprietary dried milk formula and on discharge from hospital on 6 April the total SB had fallen to 162·5 μmol/l (9·5 mg/100ml).

He was readmitted to the United Christian Hospital on 24 April because of persisting jaundice with a total SB of 162·5 μmol/l (9·5 mg/100 ml) of which 116·3 μmol/l (6·8 mg/100 ml) was in the conjugated form. Weight was 4·5 kg. The liver was palpable 2 cm below the right costal margin and spleen was just palpable. The urine was positive for bile intermittently but there was no excess urobilinogen on qualitative testing; there were no reducing substances. Amino-acid chromatography was normal. Hb was 10·6 g/dl; white cell count 13·0 × 10^9/l; neutrophils 15%; lymphocytes 75%; monocytes 8%; eosinophils 2%; reticulocytes 2·6%; platelets 490 × 10^9/l. Direct Coombs's test was negative. Red cell fragility normal. ESR (Westergren) 6 mm/1st hour. Blood films were negative for Hb H granules. The stools were normal in colour and consistency.

The patient was transferred to Queen Mary Hospital on 7 June. The results of serial liver function

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tests between 14 June and 10 July are shown in Table 1. Other investigations included: HBsAg negative; serum α-fetoprotein not increased; α-l-antitrypsin 3·6 mmol/min per litre (normal 2·6–3·5); serum thyroxine 108 nmol/l (8·4 μg/100 ml); IgM 1·22 g/l; IgG 6·15 g/l; IgA 1·50 g/l. Prothrombin time on 14 June and 19 June 11·8 seconds (control 12·0) and 10·5 seconds (control 11·3); partial thromboplastin time 50·0 seconds (control 32·2) and 46·0 seconds (control 31·1). Antibody titres on two occasions two weeks apart showed no evidence of infection with toxoplasma, cytomegalovirus, rubella virus, or herpes simplex. The bromsulphthalein (BSP) test (5 mg/kg) showed 22·9% retention at 30 min, 19% at 60 min, and 30·9% at 120 min.

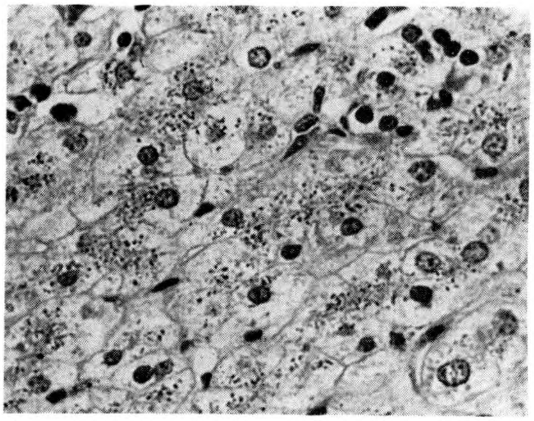

Figure *Granular pigment in liver cells. Note swollen cell just above centre of picture and 2 foci of haematopoiesis at the upper right hand corner. Binucleation and mild nuclear pleomorphism are also demonstrated. PAS after diastase with orange filter × 384.*

A Menghini needle liver biopsy on 20 June showed a specimen that was dark green in colour. Histological preparations showed that the liver had a normal lobular pattern. Most of the hepatic cells contained a brown, granular, iron-negative, non-acid fast, PAS-positive (after diastase), golden-brown fluorescent cytoplasmic pigment (Figure). Many cells also contain a little iron pigment. There are some cells with canalicular cholestasis, slight ballooning, binucleation, and variation in nuclear size. Other findings are minor and include negligible extramedullary hematopoiesis, a few mononuclear leucocytes in some portal areas, as well as iron pigment, and pigment with above-described characteristic in Kupffer cells.

Table 1 *Serial liver function tests on the proband*

	14 June	*19 June*	*27 June*	*10 July*
Total bilirubin *C – up to 26 μmol/l	119·7	121·4	80·4	58·1
Conjugated bilirubin C – up to 7 μmol/l	106	111·2	70·1	47·2
Alkaline phosphate C – 35 – 115 μmol/min per litre	1067	738	350	308
Serum AST C – 13 – 20 μmol/min per litre	94	42	56	38
Serum ALT C – 6 – 29 μmol/min per litre	37	34	61	30
Albumin C – 31 – 51 g/l	46	43	43	42
Globulin C – 23 – 40 g/l	19	20	23	23

*C—Normal values in Chinese in Queen Mary Hospital laboratory. *Conversion: SI to traditional units*—bilirubin: 1 μmol/l=0·0585 mg/100 ml.

An intravenous cholecystogram (0·6 ml Biligrafin/kg) when the total SB was 58 μmol/l (3·4 mg/100 ml) failed to show any visualisation of the gallbladder up to 4 hours.

During his stay in hospital the infant fed well and gained weight normally (6·0 kg aged 15 weeks). The icterus gradually lessened (Table 1) and the mild hepatosplenomegaly receded. The urine showed bile pigment initially but Erlich's aldehyde test repeatedly failed to show excess urobilinogen. The stools remained normal in colour and consistency throughout.

Table 2 *Liver function tests on the proband and other members of the family*

	Proband (12 weeks)	*Father (43 years)*	*Mother (33 years)*	*Sister (11 years)*	*Brother 1 (10 years)*	*Brother 2 (6 years)*
Total bilirubin (μmol/l)	119·7	20·8	17·1	17·1	59·9	58·1
Conjugated bilirubin (μmol/l)	106	8·6	0	0	35·9	27·4
Alkaline phosphatase (μmol/min per litre)	1067	50	70	405	336	329
Serum AST (μmol/min per litre)	94	18	24	18	21	26
Serum ALT (μmol/min per litre)	37	9	25	9	9	13
BSP % retention						
30 min	22·9	2·7	0	15·1	5·6	10
120 min	30·9	0	0	0	10	17·5

Conversion, see footnote to Table 1.

Family study

Both father (43 years) and mother (33 years) are ethnic Chinese and in good health; neither has a history of jaundice. There is no history of jaundice in the father's brother or 4 sisters, nor in the mother's 4 brothers. Their 11-year-old daughter has no history of jaundice and shows no abnormality on clinical examination. Their 10-year-old son had neonatal jaundice which persisted for longer than one month. Since then he has been subject to attacks of abdominal pain, nausea, and anorexia. Clinical examination showed a well developed boy with scleral icterus as the only abnormality. The younger 6-year-old brother had no history of jaundice but clinical examination detected undoubted scleral icterus. The results of biochemical tests on members of the family are shown in Table 2. Liver biopsy on the children was not regarded as justifiable. Unfortunately the grandparents were not available in Hong Kong.

Discussion

The presence of 'lipofuscin-melanin' pigment in the liver cells of the proband and the abnormal BSP tests in the proband and his two older brothers, who demonstrated scleral icterus, are compatible with a diagnosis of the Dubin-Johnson syndrome (DJS). Rotor's syndrome (RS) can be excluded on the liver biopsy finding of pigment deposition. There are, however, several features in the proband which are not typical of DJS. Most patients have first presented in adolescence or adult life, often with abdominal discomfort, nausea, and tiredness (Dubin, 1958; Shani *et al.*, 1970). Onset in the first 48 hours of life is exceptional, although this was the case in a Japanese neonate (Kondo *et al.*, 1975). The initial high SB levels are also atypical but they might be explained on the assumption that an early, presumably unconjugated, hyperbilirubinaemia may have been aggravated by DJS. More significant, perhaps, was the finding in the liver biopsy that while most of the cytoplasmic pigment was 'lipofuscin-melanin', some was apparently iron, whereas in typical DJS all of the pigment is 'lipofuscin-melanin'. The presence of some intrahepatic cholestasis is also not an expected finding in DJS. A possible explanation for these findings might be that this infant had a concomitant nonspecific cryptogenic nongiant cell hepatitis, particularly as there can be considerable variation in the histological appearances in neonatal hepatitis (Talbot and Mowat, 1975) and, at least in patients with α-l-antitrypsin deficiency, subclinical 'biochemical' hepatitis has been demonstrated (Sveger, 1976). The raised alkaline phosphatase and mildly raised transaminase levels could have a similar explanation although the normal ranges for these values in Chinese newborn infants are not known. On the other hand, some increase in the levels of alkaline phosphatase and transaminases have been reported in other cases of DJS (John and Knudtson, 1956; Dubin, 1958; Shani *et al.*, 1970).

None the less, the results of the BSP tests in the proband and his two male siblings are characteristic of DJS, in particular the secondary rise in BSP concentration at 120 min (Mandema *et al.*, 1960; Arias, 1961; Shani *et al.*, 1970). This pattern of BSP excretion is commonly regarded as diagnostic of the group of familial nonhaemolytic jaundice with conjugated bilirubin in the serum and it is, in fact, the only test which almost invariably gives abnormal results in these disorders (Shani *et al.*, 1970). It has been said not to be found in patients with other liver diseases (Mandema *et al.*, 1960). It would appear that while the uptake of BSP by the liver is normal in the DJS, after attaining saturation point the serum concentration falls more slowly than in normal subjects and after 30–45 minutes again increases so that the value at 120 minutes exceeds that seen at 30–45 minutes. This has been shown to be due to an impairment in the biliary excretion of conjugated BSP and related to a defect in the process by which BSP is transported from the liver cells to the bile. More detailed information can be obtained by sophisticating the BSP test to measure Tm (maximal transport rate) for BSP which is markedly reduced, whereas the relative storage capacity is normal in DJS (Wheeler *et al.*, 1960; Arias, 1961). We were unable to measure these values in the proband because of the volumes of blood which would have been required. The other characteristic but not invariable feature in DJS is absence of visualisation of the gallbladder on cholecystography (Dubin, 1958). This was the finding in the proband in our family, but its significance in the presence of a SB level of 58 μmol/l must be somewhat uncertain. Decreased levels of prothrombin and factor VII have also been reported in DJS (Seligsohn *et al.*, 1970) although in the proband in our family the prothrombin and plasma thromboplastin times were normal.

We believe that the cases in our family should be regarded as examples of DJS, and there is good evidence that the syndrome as originally described by Dubin and Johnson (1954) is but one end of a spectrum of disorders all characterised by a common functional defect in the transport of bilirubin and other substances from the liver cells to the bile. For example, Arias (1961) reported typical cases of DJS with abundant cytoplasmic pigment and of RS with complete absence of intracellular pigment in two brothers. Butt *et al.* (1966) studied 128 of 242 members of a family in which the classical findings of DJS were present. Pigmentation of hepatic cells was found in only 29 of 39 members who submitted to liver biopsy, but there was no correlation between the amounts of liver pigment and the increases in SB or BSP retention. In 8 members of two Puerto Rican families with jaundice of the DJS variety, Wolf *et al.* (1960) found a striking variation in the amount and distribution of the abnormal pigment. Furthermore, when the accumulation of pigment was slight, jaundice could still be present even without abnormal BSP retention and with normal visualisation of the gallbladder on cholecystography. While delay in the excretion of conjugated BSP with reflux of BSP in the conjugated form into the serum appears to be characteristic of DJS and is related to a defect in the canalicular membrane separating hepatocyte cytoplasm from canalicular bile (Schoenfield *et al.*, 1963), Schiff *et al.* (1959) reported a case of RS in which the BSP retained in the blood was all in the unconjugated form so that in this disorder there would appear also to be a defect in the plasma membrane separating hepatocyte cytoplasm from sinusoidal blood (Edwards, 1975).

The known coexistence of DJS and RS in one family (Arias, 1961) makes it likely that these disorders are variable manifestations of the same mutant gene, and the most generally held view has been that inheritance is in autosomal dominant fashion (Beker and Read, 1958; Mandema *et al.*, 1960; Butt *et al.*, 1966). However, while Butt *et al.* (1966) favoured autosomal dominance they also suggested that the proband in their large family and perhaps one or more of her siblings may have been homozygous for the gene whereas all the other subclinically affected persons were heterozygotes. Pereira Lima *et al.* (1966) concluded from a study of six generations of a family in which 3 members had RS, that an autosomal recessive gene was involved. On the basis of pedigree data obtained on 89 patients of 58 DJS sibships Shani *et al.* (1970) concluded that, at least in Iranian Jews, the mode of inheritance is autosomal recessive. More recently, Shani *et al.* (1973) have extended their study to 114 patients from 63 unrelated kindreds (34 Iranian) with extremely strong support for an autosomal recessive mode of inheritance, and showing a remarkably high rate of consanguinity among the parents in these kindreds. Edwards (1975) reported on the families of 44 American patients who fulfilled strict criteria for DJS. Parental consanguinity was found in at least 11 cases. He also concluded that DJS is inherited as autosomal recessive on the grounds of high frequency of consanguinity, the incidence of the syndrome among siblings of propositi, and the lack of involvement of more than one generation within each family. Edwards (1975) suggested that reports of cases inherited as autosomal dominants were probably due either to erroneous diagnoses of propositi or their relatives, or to pseudodominant inheritance of the recessive trait where an affected homozygous parent is married to an unaffected heterozygote. In our family the presence of three affected children of apparently normal parents is also compatible with an autosomal recessive inheritance. It is interesting to speculate whether the marginally raised level of conjugated bilirubin in the father's serum (8·6 μmol/l) might reflect heterozygosity for the gene.

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Carrier detection in Duchenne muscular dystrophy

Evidence from a study of obligatory carriers and mothers of isolated cases

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SUMMARY The mean levels of serum creatinine phosphokinase (CPK) were studied in three groups of women: normal controls (57), obligate carriers for Duchenne muscular dystrophy (30), and mothers of isolated cases of this disease (35). The distribution of the levels in these groups was significantly different and was in keeping with the hypothesis that one-third of isolated cases result from new mutations. The control and carrier ranges overlapped considerably, with the level of CPK of 33% of obligate carriers coming within the 97½ centile of the normal range. Odds against an individual being a carrier were derived for specific mean values of CPK. They should be considered with genetic information using Bayes's theorem. The mean CPK levels in obligate carriers showed significant familial clustering. This may have implications in carrier detection.

The primary metabolic defect in Duchenne muscular dystrophy remains unknown, but a raised level of serum creatinine phosphokinase (CPK) has until now been the best available method for detecting the female carrier in this disease (Schapira *et al.*, 1960). The fact that carrier and normal ranges overlap makes the interpretation of values within the normal range difficult, even when biochemical and genetic information is integrated. The mothers of isolated cases are a particular problem, and it has been suggested (Roses *et al.*, 1976) that almost all such women are carriers, although genetic theory and the results of CPK studies do not confirm this.

The present work, based on a population study of Duchenne muscular dystrophy in Wales, assesses the efficacy of the serum CPK in carrier detection, and re-examines the problem of the proportion of isolated cases which represent new mutations. The evidence for familial correlation of CPK levels in carrier women, which is of considerable practical consequence in genetic counselling, is also investigated.

Methods

All families in Wales known to contain at least one member with Duchenne muscular dystrophy were investigated as part of a more general genetic study of the disorder in Wales in which complete ascertainment was attempted. 75 such families have so far been studied. Patients were diagnosed as having Duchenne muscular dystrophy if they had had a severe disability before age 12 years and had greatly increased serum CPK, in addition to the recognised clinical features of the disease. Great care was taken to differentiate families with the Becker form of X-linked dystrophy.

Three groups of women were studied: (1) obligate carriers, a woman with at least one son and one other male relative affected or with two or more affected sons; (2) mothers of isolated cases; (3) healthy nonpregnant female volunteers of comparable age range.

Three separate blood samples were taken from these women with at least 3 days' interval between each venepuncture. Only one sample could be taken from 3 elderly obligate carriers. We did not investigate girls under 15 years. All blood samples were taken under conditions of normal activity, and heavy exercise during the preceding 24 hours was avoided. All CPK levels were determined on an Unicam SP 1800 recording spectrophotometer by the Boehringer (Mannheim) UV-System 10 assay

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method by one of us (R.J.T.). Blood samples were either separated within 2 hours and assayed directly or were stored at 4°C overnight. This made no significant difference to the recorded activity. Care was taken to protect sera from light.

Results

We studied the mean of the 3 serum CPK values for each woman. The distribution of CPK levels in normal controls (57), obligate carriers (30), and mothers of isolated cases (35) is shown in the Figure. From these distributions it can be seen that the normal range and the range for obligate carriers overlapped to a great extent. Approximately 33% of obligate carriers came within the 97½ centile for normal range. Three of our control women had mean CPK values of at least 100 mU/ml. The distributions are not gaussian but if logarithmic CPK values are used they approximate to a distribution of this form, with the means and SDs as shown in Table 1.

The odds against an individual being a carrier can be derived for specific values of serum CPK, and are shown in Table 2. They can be combined with the genetic odds and other information using Bayes's theorem, enabling precise odds to be given for values of CPK within the normal range. Details of the working of these calculations can be found in textbooks of medical genetics, such as Emery (1976).

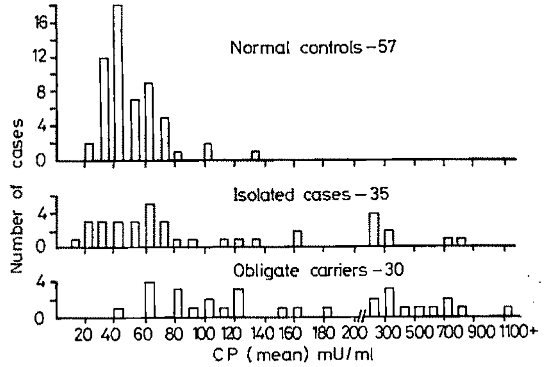

Figure *Distribution of serum CPK levels in normal controls, isolated cases, and obligated carriers.*

Table 1 *Means and standard deviations of cases*

	No. of cases	*Geometric mean*	*Mean log CPK*	*SD log CPK*
Normal controls	57	49·8	1·698	0·147
Obligate carriers	30	188·1	2·274	0·426
Mothers of isolated cases	35	83·9	1·924	0·417

Table 2 *CPK (mean of observed values) and likelihood ratio for carrier status*

Range of CPK	*LR*	*Range of CPK*	*LR*
<40	8·221	120–	0·0782
40–	8·033	130–	0·0398
50–	6·103	140–	0·0204
60–	3·831	150–	0·0106
70–	2·167	160–	0·00553
80–	1·157	170–	0·00292
90–	0·598	180–	0·00156
100–	0·305	190+	<0·001
110–	0·154		

LR = likelihood ratio.

Take for instance the case of a daughter of a known carrier. She has a prior probability of being a carrier herself of one in 2. However, information from CPK values, and any normal sons she has must also be considered. If she for instance had a mean CPK of 45 mU/ml, and a normal son, odds of approximately one in 8 for CPK value, and one in 2 for the normal son must be combined with the prior probability. Using Bayer's theorem this gives a final probability for this woman being a carrier of one in 17, significantly from the one in 2 original figure.

The CPK values for the three groups of women we studied differ significantly. Comparing normal controls with obligate carriers $t = 7{\cdot}20$ $P<0{\cdot}001$, and normal controls with mothers of isolated cases $t = 9{\cdot}09$ $P<0{\cdot}004$. If obligate carriers are compared with mothers of isolated cases $t = 3{\cdot}34$ $P<0{\cdot}002$.

The mean serum CPK values of the 30 obligate carriers is shown in Table 3 arranged within families. The ratio F of between family variance to within family variance based on logs of means of replicates is 3·96 $P<0{\cdot}05$. There is thus a significant familial clustering of CPK values.

Table 3 *Mean CPK levels in obligate carriers, arranged in families*

Family code	*Mean CPK (mU/ml)*	*Family code*	*Mean CPK (mU/ml)*
D2	187	D34	244
	122	D35	116
D3	60	D36	84
	48	D41	764
D5	438	D44	65
	159		61
D8	82		64
D9	519		162
D11	128	D45	123
	304	D46	100
	387	D47	246
D13	109	D48	90
	80	D49	627
D26	879		2300
D28	335	D60	773

Discussion

Several methods have been suggested for detecting carriers of Duchenne muscular dystrophy. Changes in muscle histology and histochemistry have been noted in some carriers, but many have given normal results. There is less discrimination between normal subjects and carriers than with serum CPK estimations. Qualitative electromyography is not of value in carrier detection; however quantitative work does show some discrimination but this method does not appear to improve the accuracy of detection based on serum CPK estimations. There is no suitable marker gene close enough to the Duchenne locus on the X chromosome to be of value in linkage work, and there is a greater overlap in other serum enzyme levels between normal subjects and carriers than with serum CPK estimations. Thus although this CPK method is far from ideal no better alternative is available. The subject has been reviewed by Emery (1969) and Gardner-Medwin *et al.* (1971).

Other workers as well as ourselves have found that control and carrier ranges of CPK values overlap greatly (Table 4). This overlap may represent variable X chromosome inactivation in the heterozygous females, as well as lack of relationship of the test to the primary biochemical defect of the disease.

We found the calculation of the odds of a woman being a carrier of Duchenne dystrophy at a certain CPK value within the normal range adds considerably to the precision of genetic counselling, as have the studies of Emery (1969) and Dennis *et al.* (1976). These odds must be combined with gentic information by the use of Bayes's theorem.

Roses *et al.* (1976) suggested, based on the study of phosphorylation of red-cell membrane proteins, that the mothers of almost all isolated cases are carriers, possibly as a consequence of unequal mutation rate between the sexes. The distribution of CPK values of the three groups of women we studied (obligate carriers, mothers of isolated cases, and normal controls) differs significantly, which argues strongly against this hypothesis. Our results are compatible with the classical genetic hypothesis of Haldane (1935) that one-third of isolated cases in a lethal X-linked recessive disorder are the results of new mutations. If this hypothesis is correct, mothers of isolated cases in our series should have a mean log CPK of 2·082 with a SD of 0·445. The values of CPK in these women are compatible with this, and give no grounds for rejecting the classical hypothesis. The implications for genetic counselling for families of isolated cases are considerable. Pickard and his colleagues (1978) recently presented data on lymphocyte capping on a variety of neuromuscular conditions, including mothers of boys with Duchenne dystrophy. They suggested that new mutations may be more common than Haldane thought. However they have not clearly differentiated obligate carriers on family history from mothers of isolated cases, nor have they analysed statistically the differences between these two groups of women and normal controls. Furthermore they did not state whether their normal controls are women of child-bearing age or not.

Our results show that correlation within families may exist for levels of CPK in carriers; this has important implications in carrier detection. Thus a relatively low CPK level in a potential carrier where obligate carriers in the family are also known to have a low CPK level may need to be interpreted with caution. More extensive data on families with multiple obligate carriers will be required to assess accurately the degree of such correlation and to allow it to be used with other information.

We thank the paediatricians, neurologists, and other clinicians in Wales who have allowed us to study their patients, and the families themselves for their cooperation. We acknowledge gratefully support given to one of us (P.S.H.) by the Muscular Dystrophy Group of Great Britain. We thank members of the Llandough Ladies' Circle, and members of the staff at the University Hospital of Wales for being controls.

Table 4 *Data on obligate carriers with CPK levels lying outside normal range in some previous series*

Series	*Normal controls (No.)*	*Obligate carriers (No.)*	*Obligate carriers with CPK levels outside normal range (%)*
Wilson *et al.* (1965) updated by Dennis *et al.* (1976)	61	32	78
Thompson *et al.* (1967)	90	37	65
Emery (1969)	107	34	53
Thomson (1969)	Not stated	11	81
Gardner-Medwin *et al.* (1971)	34 (including 9 males)	35	57
This series	57	30	67

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Cytomegalovirus and blood transfusion in neonates

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SUMMARY A fatal case of neonatal cytomegalovirus (CMV) infection attributed to exchange transfusion is described. The incidence of CMV transmission by exchange and other neonatal transfusion was studied, and the use of CMV antibody-free blood for these procedures was shown to be effective in preventing CMV infection in neonates.

Cytomegalovirus infection is a well recognised complication of blood transfusion, leading in some cases to the post-transfusion syndrome. Recent studies have shown that about 25% of exchange transfused neonates become infected with cytomegalovirus (CMV), and although transfusion-acquired CMV infection in infants seldom causes obvious illness, it may do (Yeager, 1974; Tobin *et al.*, 1975; Pass *et al.*, 1976).

An infant born in Oxford apparently died from CMV infection after transfusion. We describe this fatal case and report the results of our studies into the effectiveness of CMV antibody-free blood in avoiding transfusion-acquired infection.

Patients and methods

Between April 1975 and October 1976, 80 surviving babies were transfused in the special care unit at the John Radcliffe Hospital; 64 of them were followed up. 18 received exchange transfusions of between 200 and 1500 ml blood (mean 550 ml). The blood used was less than 4 days old and preserved in acid-citrate-dextrose. 46 received simple transfusions of between 5 and 150 ml (mean 30 ml). Initially blood for simple transfusions was obtained from 'walking donors' who were staff members of the special care or maternity units. The blood was taken into a sterile heparinised syringe and given straight to the baby. During the last 6 months of the study most simple transfusions were of CMV antibody-free blood from the Oxford Regional Transfusion Service supplied in 50 ml minipacks (Gunson *et al.*, in preparation), between one and 7 days old.

42 babies were studied retrospectively and 22 prospectively. The retrospective group were seen at least once between ages 10 weeks and 14 months, at which time the babies were physically examined and their development, head circumferences, and hearing were assessed. Blood for CMV complement-fixation tests and immunofluorescent antibody (de Silva *et al.*, 1977) was taken from both mother and baby, and a throat swab and urine were taken from the baby for virus isolation on human embryo fibroblast cultures. In the prospective group blood was taken from the mother within 2 weeks after transfusion of the baby, and a throat swab and urine were collected from the baby for virus culture within 3 days of transfusion. The mothers and babies in this group were seen again between 3 and 6 months after transfusion, and 8 of them were seen a second time at between 6 and 9 months; at these times the baby was clinically assessed and a throat swab, urine, and blood were taken for virus investigation as in the retrospective group.

All the 42 babies studied retrospectively received blood from donors who had not been screened for CMV antibody, although subsequently the CMV antibody titres of all blood donors were determined for 33 of the babies. For the remaining 9 babies the CMV titre of at least one donor could not be ascertained. In the prospective group of 22 babies one or more donors for 3 babies were not available for CMV serological tests. 16 babies were given CMV antibody-free blood deliberately.

97 infants aged between 5 and 18 months, who had not been transfused and who were attending an infant welfare clinic, or were in hospital, served as controls; they were tested for CMV infection either by virus isolation or serology.

Results

In the first 13 months of the study, before a policy of selection of CMV-negative donors was introduced,

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Table 1 *CMV infection after neonatal blood transfusion*

Study	*Type of transfusion*	*No. tested*	*No. infected*	*Virus isolation*	*Antibody production*	*Infected (%)*
Retrospective	Exchange	16	4	3	4	25
'Untested blood'	'Top up'	32	4	4	4	12·5
Prospective	Exchange	2	0	0	0	0
CMV-free blood	'Top up'	14	0	0	0	0
Controls, not transfused	Infants (5–12 months)	42	2	2	NT	4·8
	Infants (5–18 months)	55	2	NT	2	3·6

NT = not tested.

4 (25%) of 16 exchange transfused babies and 4 (12·5%) of 32 receiving simple transfusions became infected with CMV. During the last 5 months of the study, the 2 babies exchange transfused and all 14 receiving simple transfusions of CMV antibody-free blood remained uninfected (Table 1).

The blood donor CMV status was determined by immunofluorescence (IF) (de Silva *et al.*, 1977) for 52 of the 64 babies. 21 babies received blood from at least one CMV antibody-positive donor and 8 (38%) became infected, while the 31 babies who received only CMV antibody-free blood remained uninfected. Comparing these two groups by the χ^2 test the result was significant ($\chi^2 = 11·54$, $P<0·001$). None of the 12 remaining babies who received blood from a donor of unknown CMV status became infected. The CMV infection rate by donor antibody status in those exchange transfused is given in Table 2.

Exchange transfusions. The 4 babies who became infected after exchange transfusions received on average 864 ml blood from 4 donors for each baby, compared with an average of 480 ml from 2 donors for those 14 uninfected. Three of the 4 babies infected after exchange transfusion showed no clinical signs attributable to CMV during the period of observation. The 4th, who subsequently died, is described below.

Case report

A 33-year-old group O Rhesus-negative mother who had previously had 3 liveborn babies and one stillborn baby affected by rhesus iso-immunisation, became pregnant again with a rising Rh antibody titre during the 2nd trimester. She refused intrauterine transfusion and underwent plasmapheresis, a total of 50 units of plasma being exchanged over 10 weeks. The Rh antibody level remained fairly steady and she was delivered by caesarean section at 30 weeks' gestation. She had received a 40-hour course of betamethasone since an amniocentesis 3 days before delivery had shown the amniotic fluid palmitate to be 19 mmol/l. Her baby daughter weighed 1300 g at birth and had an enlarged liver and spleen, but was not hydropic. The baby's blood group was O Rh positive, her cord plasma bilirubin was 100 µmol/l (6 mg/100 ml), haemoglobin 7·3 g/dl, reticulocytes 30%, and the direct Coombs's test strongly positive. She was given 4 exchange transfusions during the next 2 days through an umbilical venous catheter with 0–2-day old, partially packed ACD blood. Phototherapy was given for the first 3 days of life and the bilirubin level had fallen to 70 µmol/l (4 mg/100 ml) by day 6. Twelve hours after the last exchange transfusion she was given 5 ml platelet concentrate and 30 ml fresh heparinised blood as she had rectal bleeding and a platelet count of 39×10^9/l. Feeds of expressed breast milk were gradually introduced 5 days after the onset of the rectal bleeding, and although she required IV alimentation for 9 days, she apparently made a complete recovery from her haemolytic disease by the 12th day of life.

Table 2 *CMV infection in exchange transfusions according to donor antibody status*

CMV antibody status of donors	*No. of babies tested*	*Infected babies*	
		No.	*%*
+	7	3	36
UK*	4	1	
−	7	0	0

*Unknown.

Six days later she became mottled and less active and her temperature became unstable. She was treated with gentamicin, cloxacillin, and carbenicillin, although bacteriological reports subsequently showed no pathogens. The antibiotics were changed to chloramphenicol and penicillin when her condition did not improve. Her white blood count rose to $45·3 \times 10^9$/l on the 24th day of life, with $15·4 \times 10^9$/l neutrophils, $18·1 \times 10^9$/l lymphocytes, and $10·8 \times 10^9$/l eosinophils.

On the 27th day she was noted to be jaundiced and her liver and spleen again became enlarged. Her total bilirubin rose to 425 µmol/l (25 mg/100 ml) with 200 µmol/l (11·5 mg/100 ml) conjugated. Her aspartate transaminase was 970 IU/l, lactate dehydrogenase 3900 IU/l, and alkaline phosphatase 165 IU/l. Hepatitis B antigen was not detected, but CMV was isolated from urine and a throat swab taken at 23 days of age, and from CSF taken 8 days later. Her condition steadily deteriorated. She developed gross ascites and anaemia, her plasma sodium level fell, and she became hypoalbuminaemic. Her platelet count fell and she developed haematuria and a petechial rash. She became oliguric and despite treatment with albumin, blood transfusions, frusemide, and physiological doses of hydrocortisone, she died at age 28 days. Permission for necropsy was not obtained.

The mother's blood taken at 20 weeks' gestation and at delivery contained CMV IgG antibodies at a titre of 1:64 but no specific CMV IgM or IgA was detected in either specimen. The baby's cord blood total IgM was <25mg/100 ml (<30 IU/ml) but none was available for testing for specific CMV antibodies. Three of the 4 blood donors for the exchange transfusions were found retrospectively to be CMV antibody positive. The donor of a small blood transfusion given on day 5 was also CMV positive. The CMV antibody status of the platelet donation was not determined.

Simple transfusions. The 4 babies who became infected after simple transfusions showed no clinical signs of infection. At follow-up between 5 and 13 months of age, 3 were still excreting virus and all had antibody to CMV. Three were normal on examination. The 4th was mildly retarded, probably as a result of repeated severe apnoeic attacks after delivery at 28 weeks' gestation.

Maternal CMV infection. Sera from 6 of the 8 mothers of infected babies were available for testing from late pregnancy and again when the babies were seen for follow-up. Five of these mothers had antibody to CMV before delivery, 4 of whom showed no change in titre. One showed a 16-fold rise in complement-fixation titre from 1:8 to 1:96 at 8 months after delivery, indicating reinfection or reactivation of her previous CMV infection. The 6th mother who had no CMV antibody before delivery showed a raised titre (1:32) when tested 5 months postpartum.

Discussion

Although cytomegalovirus infection after blood transfusions usually produces no clinical disease, in a few patients it can produce post-transfusion mononucleosis (Foster and Jack, 1969), and this syndrome can occur at any age including the first few weeks of life (Tobin *et al.*, 1975). Cytomegalovirus infection can however be accentuated by immunosuppression, especially in patients undergoing renal and other transplants in whom primary infections can cause worrying symptoms and may occasionally lead to a fatal outcome. It is also an occasional complication in leukaemic and lupus patients and in others on immunosuppressive treatment.

It cannot be absolutely certain that the fatal case reported here acquired CMV infection from blood transfusion. However, there was no serological or other laboratory or clinical evidence that this was a congenital infection; the mother had neither IgA nor IgM CMV antibodies at any time during pregnancy and the isolation of virus from urine, throat swabs, and CSF during the illness would indicate a generalised viraemia in the baby.

Although the neonate usually does not seem to be any more likely to produce overt symptoms after CMV infection from transfusion than older people, such babies may be a danger to their mothers who usually are infected by them during the ensuing months. If these mothers happen to be pregnant and nonimmune, it is possible that the fetus could be affected by cytomegalic inclusion disease. As the usefulness of transfusion with CMV-free blood is still open to discussion, evidence on the effectiveness of screening blood for CMV antibody, and the demonstration that infection can be so prevented by its use are worth while.

For CMV antibody determination we used the IF antibody test (de Silva *et al.*, 1977) as it is more sensitive than the complement-fixation (CF) test and quicker to perform, a result being obtained in 2 hours as opposed to the overnight incubation required for the CF test. Our results using this IF test in exchange transfused babies indicates that it is satisfactory for blood screening. Although the numbers are not great, the difference between those infected after receiving CMV-positive blood and those not infected after negative blood was significant.

It is obvious that all blood cannot be screened for CMV antibodies by all blood transfusion centres, but we feel that there should be more studies to see if the use of CMV-negative blood in exchange transfusions of babies is worth while. These should be parallel to studies in patients undergoing transplants and heart operations where CMV infection in the nonimmune can be prevented by screening blood and kidney donors and using material only from those without CMV antibody.

We thank Miss Eileen Hopkins and her staff at the East Oxford Health Centre for specimens from infants; Dr G. R. H. Gunson, Oxford Regional

Blood Transfusion Service, for samples from blood donors; Dr D. Knight for help with the case history; and Professor J. P. M. Tizard and Dr J. D. Baum for encouragement and advice.

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The following articles will appear in future issues of this Journal:

Role of viruses and bacteria in acute wheezy bronchitis in childhood: a study of sputum. *M. E. C. Horn, S. E. Reed, and P. Taylor.*

Pulmonary hypoplasia: lung weight and radial alveolar count as criteria of diagnosis. *S. S. Askenazi and M. Perlman.*

Intrathecal serotherapy in neonatal tetanus. A controlled trial. *M. R. Sedaghatian.*

Munchausen syndrome by proxy in twins. *D. A. Lee.*

Subacute sclerosing panencephalitis after drug-induced immunosuppression. *J. B. S. Coulter, N. Balch, and P. V. Best.*

Neonatal small left colon syndrome. *L. Rangecroft.*

Archives of Disease in Childhood, 1979, **54**, 542–544

Comparative trial of manual and mechanical percussion technique with gravity-assisted bronchial drainage in patients with cystic fibrosis

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SUMMARY Chest physiotherapy still remains one of the most important aspects in the treatment of chest complications of cystic fibrosis. A mechanical device that allows the patient with cystic fibrosis to do his own chest physiotherapy will be of great benefit if it is as effective as manual percussion. 14 patients with cystic fibrosis using mechanical and manual percussion physiotherapy were studied by measuring sputum volumes, and FEV and FVC. Results with the mechanical percussor were as good as with the manual percussor and, therefore, it would be reasonable for the older patient to use the former on his own.

The life expectancy of patients with cystic fibrosis (CF) has greatly improved in recent years (Anderson and Goodchild, 1976), and most CF clinics are now having to extend their care to the adolescent and young adult. Any patient, as he grows older, resents having to depend on another adult for chest physiotherapy. We have, therefore, compared the use of manual with mechanical percussion as the latter would enable the patient to do his own treatment and thus gain independence (Denton, 1962).

Patients and method

14 patients with CF between ages 7 and 21 years who could co-operate with the use of the Vitalograph spirometer were chosen. At the time of testing the patients were in clinical remission. 11 were normally sputum producers and 3 produced sputum only when they had exacerbations of chest infection.

Apparatus. The mechanical percussion unit, Equi-Med percussor* (Fig. 1) operates on 230 volts at 200–3200 strokes/min using a 10-speed selector switch. All the children were tested using 230 strokes/min. The percussor weighs 1·588 kg. The unit is applied to the chest wall, the percussor head being directly in contact with the rib cage (Fig. 2) over the selected segment of the lung to be drained.

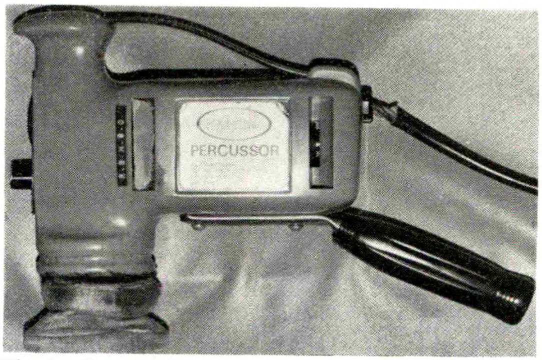

Fig. 1 *Equi-Med percussor.*

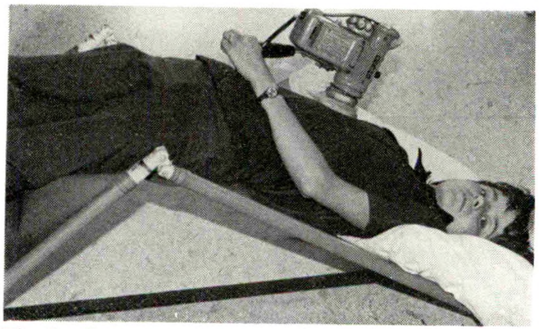

Fig. 2 *Teenage patient using the percussor.*

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*Obtainable from Medical and Scientific Computer Services Ltd, Altona Road, Lisburn, Co. Antrim, N. Ireland.

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The percussion was interrupted only for expectoration and change of position.

Experimental conditions. Patients were treated on one day with manual and the next with mechanical percussion, random sampling tables being used to determine the initial method. Each patient was treated at the same time each day. The Vitalograph readings were FEV_1, FVC, FER, the readings being taken at 10-min intervals for one hour after treatment. Amounts of sputum were measured by weight.

The postural drainage positions were those described by Kendig and Chernick (1977).

Lower lobes
Four segments, right and left, anterior, posterior, lateral, superior.

Middle and lingular lobes
Upper lobes
Two segments, right and left, anterior, apical, using a treatment time of 32 minutes for each period. The various lobes were treated in the same order in each patient and all segments were treated for a period of 2 minutes.

Table 3 *Amount of sputum in 14 patients after manual and mechanical chest percussion*

Case	Age (years)	Amount of sputum (g)	
		Manual	*Mechanical*
1	9½	8·51	15·42
2	8½	23·06	27·46
3	14¼	18·54	8·09
4	12¾	12·68	3·38
5	12½	18·54	8·09
6	12	—	—
7	7½	0·856	0·778
8	6¼	1·55	1·33
9	20½	20·34	32·26
10	21	1·81	0·71
11	7	1·5297	1·7137
12	7	—	—
13	14¼	—	—
14	8½	25·66 (vomit)	8·8413

Table 1 *FEV_1 results (in litres) in 14 patients using manual and mechanical percussion*

Case	*Age (years)*	*Manual*			*Mechanical*		
		Before	*+ 10 min*	*+ 60 min*	*Before*	*+ 10 min*	*+ 60 min*
1	9½	1·55	1·50	1·75	1·35	1·50	1·75
2	8½	0·85	0·70	0·85	0·85	0·77	0·90
3	14½	1·8	1·63	1·80	1·95	1·55	1·69
4	12¾	1·30	1·25	0·74	0·72	0·80	0·86
5	12½	1·20	0·84	1·15	1·1	1·15	0·98
6	12	1·65	1·42	1·34	1·60	1·39	1·20
7	7½	0·45	0·55	0·65	0·45	0·45	0·51
8	6¼	0·55	0·40	0·54	0·45	0·42	0·43
9	20½	0·82	0·74	0·77	0·81	0·75	0·80
10	21	2·85	2·92	2·05	1·90	2·45	2·80
11	7	0·50	0·51	0·50	0·56	0·45	0·48
12	7	1·75	1·65	1·60	1·63	1·73	1·70
13	14¼	0·55	0·44	0·40	0·6	0·60	0·75
14	8½	1·25	1·34	1·15	0·98	0·95	1·50

Table 2 *FVC results in litres in 14 patients using manual and mechanical percussion*

Case	*Age (years)*	*Manual*			*Mechanical*		
		Before	*+10 min*	*+60 min*	*Before*	*+10 min*	*+60 min*
1	9½	2·15	2·10	2·40	1·85	2·10	2·30
2	8½	1·0	0·90	1·20	1·15	1·06	1·25
3	14¼	2·30	2·20	2·30	2·50	2·15	2·20
4	12¾	1·30	1·25	1·33	1·35	1·40	1·48
5	12½	1·65	1·56	1·75	1·70	1·95	1·80
6	12	2·10	2·00	2·06	2·20	2·00	1·85
7	7½	0·07	0·75	0·90	0·72	0·55	0·70
8	6¼	1·15	1·15	1·30	1·20	1·19	1·15
9	20½	1·86	1·70	1·82	1·86	1·67	1·75
10	21	4·52	4·80	4·45	4·50	4·4	4·60
11	7	1·00	1·00	0·88	1·10	0·90	1·25
12	7	2·05	2·09	1·95	1·96	2·05	1·98
13	14¼	1·25	1·00	1·10	1·45	1·53	1·53
14	8½	1·95	1·80	1·75	1·80	1·80	2·05

Results

The FEV (Table 1) and FVC data (Table 2) show there was no obvious difference between mechanical and manual treatment, and this was confirmed by statistical analysis. Amounts of sputum are shown in Table 3. It was suggested by the parents that the children coughed up more sputum when using the mechanical percussor at home but, when the actual amounts were measured, there was no overall difference.

Discussion

All patients and all parents (with the exception of one) preferred mechanical percussion. Patients found it was less tiring and that it gave them a sense of support. Most parents admitted that they felt that they could not do the manual technique as well as the trained physiotherapist and felt the children were not gaining maximum benefit. However, they thought the children received maximum benefit with the mechanical percussor. All patients could treat some segments themselves, particularly the upper lobes. The main disadvantage for the patient was the noise of the percussor. We find that small babies adjust to the mechanical percussor and often fall asleep during treatment. The youngest child who could use the percussor independently was 13 years. Small children could not reach the basal segments of the lower lobes and found the middle lobe difficult, although they could treat the upper ones.

It would appear that mechanical is as effective as manual percussion. The percussor costs about £85 (plus VAT). This is a large sum to spend, particularly as manual percussion can be just as effective. The main advantage of a mechanical percussion unit is that a teenage or adult CF patient can use it entirely on his or her own and thus be independent.

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Serum C-reactive protein test in diagnosis of septic complications of cerebrospinal fluid shunts for hydrocephalus

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SUMMARY Serial tests for serum C-reactive protein (CRP) were carried out on 40 children undergoing cerebrospinal fluid shunt surgery, to determine the pattern of appearance and disappearance of CRP in relation to this type of operation, in the absence of postoperative complications. Samples of sera from a further 268 children, 79 of whom presented after shunt surgery with symptoms suggesting infective complications related to the shunt, were examined for CRP. The results showed that, while the test is negative in uncomplicated colonisation of ventriculo-atrial shunts, it is reliably positive in patients with colonised ventriculo-peritoneal shunts, ventriculitis, or shunt nephritis.

Tillet and Francis (1930) described a substance which was present in the sera of patients in the acute stage of pneumonia. Anderson and McCarty (1950) described the use of a capillary test for this C-substance (now called C-reactive protein, CRP) in the serum to monitor the severity of the disease in rheumatic fever, and other workers used it to assess the presence and severity of other inflammatory conditions (Bunim *et al.*, 1952). The exact nature and origin of CRP is still unclear. Immunological studies show that it is a globulin (Wood *et al.*, 1954) but little is known about its site of origin, fate, or function (Wood, 1953; Kushner and Kaplan, 1961). CRP is an abnormal protein as it is not found in the serum of a healthy person, but appears in a matter of hours after onset of tissue damage or destruction, regardless of the cause, and disappears equally rapidly after the destructive process has ceased. CRP is not subject to normal variation, as is the erythrocyte sedimentation rate (ESR), and is independent of the haematocrit. In these respects it is generally found to be more useful and sensitive than the ESR as a reflection of acute inflammatory disease.

Sera from patients with cerebrospinal fluid (CSF) shunts were tested for presence of CRP to assess its usefulness as an adjunct to other diagnostic tests for septic complications associated with the use of these devices.

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Patients and methods

308 children admitted for insertion of a first shunt, revision of an existing one, or for investigation of possible shunt complications, were studied. Their ages ranged from 2 weeks to 15 years. All had hydrocephalus and, in many, this was associated with spina bifida. In others it was posthaemorrhagic, postmeningitic, or 'congenital'.

Blood was taken from each child preoperatively and then on days 5 and 10 postoperatively. A group of 40 of these children also had blood taken on the first day after operation. Samples were routinely taken from children at these times as a means of detecting shunt colonisation by the *Staphylococcus albus* antibody test (Bayston, 1972, 1975). Many were followed up as outpatients and further blood samples taken. In this hospital the Holter valve is used exclusively and both ventriculo-atrial and ventriculo-peritoneal routes are used.

Serum CRP was measured by the capillary method (Anderson and McCarty, 1950) using commercially prepared antiserum (Difco Laboratories Ltd). To perform the test, 25 μl of patient's serum are run into a capillary tube, followed by an equal volume of antiserum. The tube is rocked to and fro to mix, and one end is plunged into a block of modelling clay. The tube is kept upright in this manner at room temperature for 8 hours or overnight. If CRP is present a complex is formed which falls to the bottom of the column of fluid in the tube. The height of the column of precipitate is measured in millimetres to give a semi-quantitative result.

Results

Of the 308 children studied, 229 did not develop any clinical abnormality or sign of shunt complications. 40 of these children had had CRP estimations carried out on samples taken on the day after operation, as well as preoperatively, and on the 5th and 10th postoperative days. 21 of these had insertion or revision of an atrial shunt, 17 had insertion or revision of a peritoneal shunt, and a further 2 had exploration of a peritoneal shunt limited to the distal end. The CRP results in these 40 children are shown in Table 1. All gave a positive test after the operation on day 1, but by day 5 the test was negative except in the 17 children in whom insertion or full revision of a peritoneal shunt had been performed. All had become negative by day 10. In the remaining group of 189 patients who did not have CRP estimations carried out on the day after operation but in whom there were no complications, all had negative CRP tests preoperatively and on the 10th day postoperatively. Of the 87 patients in this group who had full revisions of peritoneal shunts, 79 had positive CRP tests on the 5th postoperative day.

The remaining 79 children subsequently presented, either at outpatient visit or on direct hospital admission, with one or more of the signs and symptoms of shunt colonisation. The results in these children, and their final diagnoses, are shown in Table 2. Shunt colonisation caused by *Staphylococcus pyogenes* gave rise to a positive test in all 7 patients. In 8 cases of ventriculitis and 8 of shunt nephritis the CRP test was uniformly positive. 11 cases of peritoneal shunt surgery showed a different pattern of results from those shown in Table 1, in that the CRP test did not become negative by day 10 postoperatively, and was persistently positive when checked thereafter.

All 16 cases of uncomplicated atrial shunt colonisation due to *S. albus*, where there was no evidence of shunt nephritis or ventriculitis, gave negative CRP tests.

Table 1 *Serum CRP results associated with shunt surgery in the absence of complications*

	Positive CRP			
	Before operation	*After operation (days)*		
		1	*5*	*10*
Insertion or revision of atrial shunt (n = 21)	0	21	0	0
Insertion or revision of peritoneal shunt (n = 17)	0	17	17	0
Limited exploration of peritoneal shunt (n = 2)	0	2	0	0

Table 2 *Serum CRP results and final diagnoses in 79 children with suspected shunt sepsis*

Diagnostic group	*Positive* (*n*=*56*)	*Negative* (*n*=*23*)	*Subtotal* (*n*=*79*)
Uncomplicated atrial shunt colonisation (*S. albus*)	0	16	16
S. pyogenes shunt colonisation	7	0	7
Ventriculitis	8	0	8
Shunt nephritis	8	0	8
Colonised peritoneal shunt (*S. albus*)	11	0	11
Intraventricular haemorrhage	2	0	2
Urinary tract infection	6	4	10
Respiratory tract infection	9	3	12
Otitis media	5	0	5

The remaining 29 children in whom there was no evidence of sepsis of the shunt or central nervous system gave variable results.

Discussion

The CRP test has been used to monitor postoperative progress in general surgery (Fischer *et al.*, 1976), and it has other applications, but its use in shunt surgery and its subsequent follow-up has not been described. The results of the test after shunt surgery in the absence of postoperative complications are shown in Table 1, and show that CRP is also present in the serum on day 1 postoperatively. If such operations are classified into three groups, the test will give negative results by day 5 in operations on atrial shunts; it was negative in the 2 patients in whom only limited exploration of the intraperitoneal portion of the shunt was carried out. However, in the 17 patients in whom a more extensive procedure was carried out (revision or insertion of a peritoneal shunt) the test was still positive on day 5. The presence of CRP in the serum after shunt operation is presumably due to tissue damage incurred as a result of incision and dissection. To insert a catheter from the neck to the peritoneal cavity a tunnel has to be created over the rib cage with the use of much blunt dissection. This would explain the prolonged disappearance time for CRP in these cases.

In those 11 cases where the CRP test was persistently positive after operation, a diagnosis was made of colonisation of the shunt involving only the lower catheter. The children presented with signs suggesting blockage rather than colonisation (Bayston and Spitz, 1977) and the peritoneal reaction resulting from the flow of bacteria-laden CSF was found at operation to be causing partial obstruction of drainage. The reactive changes in the peritoneal cavity would explain the persistently positive CRP test.

The 7 cases of colonisation by *S. pyogenes* were all associated with postoperative infection of the scalp and/or neck wounds. Such colonisation is usually confined to the outer surface of the shunt, but because of the histolytic properties of the organism the infection rapidly tracks down the outside of the catheter and organisms enter the blood stream. There is considerable inflammatory response and it is therefore not surprising that the CRP test is positive in such cases.

However, in cases of colonisation of atrial shunts with *S. albus*, where the organisms are confined to the lumen of the shunt (Bayston and Penny, 1972) and enter the blood stream directly from the end of the distal catheter, there is no inflammatory response unless there is also involvement of the cerebral ventricles. In those uncomplicated cases without ventricular involvement, CRP is absent from the serum and diagnosis is confirmed by the finding of a positive *S. albus* antibody test.

Where the preoperative investigation of a patient includes a contrast or air ventriculogram, the finding of CRP in the serum the next day strongly suggests infective ventriculitis, and insertion of a shunt should be delayed until such infection has been ruled out, if possible by examining the ventricular fluid.

In a case of long-standing colonisation of atrial shunts, a positive CRP test often indicates the onset of shunt nephritis, even before haematuria is seen. At this stage the finding of high antibody levels to *S. albus* together with low serum complement levels confirms immune complex nephropathy.

The CRP test is nonspecific and positive results may be due to inflammation or tissue necrosis from any cause. Of 12 children whose symptoms were found to be due to a respiratory infection, 9 gave a positive CRP test. By subjective assessment, the illness in these patients was more severe than in the remaining 3. The 9 patients with positive CRP tests who had respiratory infections also had bacterial infections, whereas the remaining 3 were thought to have viral infections. Similarly the 5 cases of acute otitis media which showed a positive CRP test were found to be bacterial.

The test was also positive in 10 patients with urinary tract infection who presented with fever among their symptoms. Although precise details are not known, it is possible that those children with infection and ureteric reflux probably had renal involvement, and would be more likely to give a positive CRP test than those with cystitis alone.

As the purpose of this paper is to investigate the place of the CRP test in diagnosing septic complications of CSF shunts, the 22 children in whom CRP was found in the sera but in whom there was no involvement of the shunt may be thought of as false positives. However, if the test is found to be positive such possible causes as otitis media and infection of the respiratory and urinary tracts can be excluded easily and rapidly.

Conclusions

The results of the study suggest that the unexpected finding of CRP in the serum in a patient with a CSF shunt should always be vigorously investigated. The test is useful for detecting preoperative ventriculitis after ventriculography, and colonisation of ventriculo-peritoneal shunts. It is often the first indication of the onset of early shunt nephritis in those patients with long-standing colonised atrial shunts.

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Change of reference style

From January 1980, the *Archives* will change its style for citing references and will follow the number system. We are making this change in order to conform with the 'Vancouver style' of uniform requirements for manuscripts submitted to biomedical journals.

Previously the *Archives* has used the Harvard reference system. Its advantages and disadvantages compared with those of the number system have seemed evenly balanced, but the editors have been aware of the burden imposed on authors and their secretaries by the different styles which different journals require. Therefore, with the unanimous agreement of the editorial committee, we have decided to support a move whereby a large—and increasing—number of major medical journals will accept manuscripts presented in one agreed style.

The system numbers references consecutively in the order in which they are first mentioned in the text. References are identified in the text by arabic numerals. For further details see instructions to authors inside the front cover, and the references cited.[1,2]

From now onward all manuscripts submitted should accord with the new style.

[1] International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979; **1**; 533–535.

[2] Lancet. The Vancouver style. Uniform requirements for manuscripts submitted to biomedical journals. *Lancet* 1979; **1**; 429–430.

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Short reports

Two cases of perinatal listeriosis

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SUMMARY Two cases of neonatal listeriosis are described. The incidence in the UK is given and the treatment of the pregnant woman is briefly discussed.

Perinatal listeriosis is believed to be rare in Britain but it may be under-reported. It carries a high mortality for the child but the mother suffers only a mild illness. Two cases are described in which the infants survived. One of these is thought to be the first description of a case treated during pregnancy in this country.

Case reports

Case 1. A 35-year-old Englishwoman, married to a Greek and living in Germany attended our antenatal clinic at approximately the 35th week of her 2nd pregnancy. A previous pregnancy 6 years previously had been normal.

Admitted in early labour 8 days later her temperature was 36°C and the pulse rate 84/min. She had a spontaneous delivery of a baby girl who had difficulty in breathing. The placenta was retained and removed manually, and a postpartum haemorrhage required blood transfusion during which her temperature rose to 38°C.

Although a transfusion reaction could not be excluded clinically a course of gentamicin 80 mg intramuscularly 8-hourly was begun lest infection were present. A transfusion reaction was subsequently excluded. Unfortunately a blood culture was not taken until the next day; it showed no growth. A high vaginal swab and urine sample, also taken next day, yielded no significant organisms. Her pyrexia persisted throughout the day rising to 38·1°C with rigors. Urinary output was satisfactory and her general condition good. At this stage the patient's history was re-examined and it was found that on the day before admission she had had a temperature of 38°C with cold sweats and rigors, and she had had several 'flu-like episodes' during her pregnancy in Germany before arrival here. Her illness had been vague and there had been no diagnosis; she had been given several drugs which we could not identify. Pyrexia lasted until 2 days after delivery reaching a maximum of 39°C and then settled. There was no evidence to suggest genital tract infection and her subsequent progress was uneventful.

The baby weighed 2980 g and was assessed as 36 weeks' mature. She had Apgar scores of 1, 5, and 8 at one, five, and ten minutes respectively and had to be intubated. Her respiratory difficulties continued and blood–gas and bicarbonate studies suggested a perfusion-diffusion defect. After 16 hours she became jaundiced. As the father was Greek glucose-6-phosphate dehydrogenase deficiency was looked for and excluded. At 36 hours she developed a purpuric rash. A full infection screen was carried out including antibody screen for rubella, cytomegalovirus, measles, herpes simplex, and toxoplasma. None of these was positive and the platelet count was normal. Two separate blood cultures and swabs from the eyes, nose, throat, skin, and umbilicus all grew *Listeria monocytogenes* type 4. The CSF was sterile but contained $0 \cdot 014 \times 10^9$/l white cells, 75% polymorphs. The urine was sterile.

Once the diagnosis had been made in the baby the mother's blood was again cultured, but still with negative results. Urethral, cervical, and vaginal swabs were again negative. Serological tests carried out on the day of delivery and 15 days later each gave an agglutination titre of 2048 against *Listeria*. The placenta was not available for examination but it looked healthy and complete and weighed 700 g.

A course of flucloxacillin and ampicillin equally (Magnapen) 125 mg 6-hourly had been prescribed for the baby at 12 hours, and gentamicin 7·5 mg IM 12-hourly was added at 36 hours, and the Magnapen changed to ampicillin alone. This gave a gentamicin blood level of 5·6 mg/l one hour after injection. Gentamicin was continued for a total of 14 days and ampicillin for 28 days.

The baby's condition slowly improved and she weighed 3375 g on discharge when 36 days old. She was feeding and behaving normally for a preterm neonate. The parents who were returning to Germany were strongly advised to seek developmental follow-up by a paediatrician.

Case 2. A 31-year-old Englishwoman living in an Essex village was admitted with slight vaginal bleeding. She had not recently travelled abroad. She was 29 weeks' pregnant by dates but the uterus was 36 weeks by size. Her temperature was 37·8°C, pulse 88/min, and blood pressure 130/80 mmHg. The fetal heart rate was 156/min. She was slightly flushed but had no pain. A slight brownish vaginal discharge had been present 2 weeks before. She was mildly sedated and was kept under observation.

Next day her temperature was 38°C. The fetal heart rate varied between 148 and 140/min. At midnight she had a slight bright red blood loss and a further rise in temperature to 38·8°C. Blood, urine, and a high vaginal swab were taken for culture. That night she passed a small blood clot and in the morning her temperature was 39°C and WBC $9 \cdot 3 \times 10^9$/l (85% polymorphs). Ultrasound scan excluded placenta praevia. Vaginal examination with a speculum showed an acutely inflamed, very vascular, and friable cervical polyp; a diagnosis of possible carcinoma of the pregnant cervix was made. Cytology showed only inflammatory cells. It was decided that the polyp should be removed for histology and, preparatory to this, ampicillin 500 mg 6-hourly IM for one day, followed by 500 mg 6-hourly orally with 1 g per day of probenecid was prescribed. Next day she was apyrexial but the blood culture showed *L. monocytogenes* type 1/2, so gentamicin 80 mg 8-hourly IM was added and the probenecid stopped. No growth of *Listeria* or other significant organism was obtained from the high vaginal swab or urine but these cultures were only held for 24 hours. A serum gentamicin level of 2·9 mg/l one hour after injection was obtained.

After one week's treatment, during which the patient remained apyrexial and fetal movements were vigorous, the polyp was removed. Histologically there was no evidence of malignancy but mild inflammation was present. Gram tissue stain showed no organisms, and no growth was obtained either from the polyp or from vaginal swabs taken at operation.

The next day gentamicin was stopped but ampicillin, again with probenecid, continued. Four days later the patient spontaneously delivered a healthy child. Ampicillin was discontinued next day having been given for a period of 14 days.

Serological tests showed an agglutination titre of 32 against *L. monocytogenes* on the day of delivery and again 15 days later.

The baby girl weighed 2155 g and was assessed as 37 weeks. No difficulty was experienced during delivery and she had an Apgar score of 8 to 9 at one minute and 10 at five minutes after delivery. She had no respiratory difficulty and no problems apart from low birthweight. She fed well and gained weight normally.

Listeria was not isolated from her nose, eyes, throat, or umbilicus on delivery nor was it isolated from the liquor amnii or placenta. Blood and CSF cultures were sterile. She was not given systemic antibiotics but was carefully watched for development of any respiratory or neurological signs.

Discharged at 23 days paediatric follow-up has shown normal development at the 3-month stage and should continue.

The placenta weighed 450 g and the histology showed moderate intervillous fibrin deposition and focal calcification. One area of pyogenic abscess formation in an ischaemic infarct was seen and may well reflect bacterial colonisation of an infarct. No organisms were seen.

Discussion

Only 14 cases of neonatal listeriosis have been described in the UK (Edmunds *et al.*, 1957; Barrow and Pugh, 1958; Moore and Whitmore, 1960; Harding and Brunton, 1962; Barber and Okubadejo, 1965; Coleman, 1965; Jellard and Churcher, 1965; Beck *et al.*, 1966; Scott and Henderson, 1968; Kite, 1975), and one other case is known from personal communication (D. Robson and R. N. Peel, 1976). Between 1967 and 1972, 47 cases of listerial infection in children under one year were reported to the Public Health Laboratory Service of which 14 were fatal, but the data do not say how many were neonates. Between 1972 and 1975, 24 neonatal cases were reported of whom 9 recovered and the outcome was not recorded for 6. In 1977 at least 4 out of 11 neonates died. A mortality rate of 91% for babies has been recorded in Canada (Sepp and Roy, 1963). Occasionally the child is several months old when meningitis supervenes (Wright and Macgregor, 1939; Edmunds *et al.*, 1957; Turner *et al.*, 1958).

There have been several small outbreaks in Germany (Seeliger *et al.*, 1969) and one in New Zealand (Becroft *et al.*, 1971). Infection of the mother is usually thought to occur by ingestion of contaminated food or possibly by sexual intercourse leading to either transplacental or transmembranous infection of the fetus (Robertson, 1977) from the mother's blood stream or faeces. Case 1 gives a typical antenatal history, and the bleeding polyp in Case 2 was a possible portal of entry for the organism from the vagina to the mother's blood. Hospital crossinfection of babies was a possibility in Sweden (Larsson *et al.*, 1978), but this could not be so in these two cases as the illnesses were caused by different serotypes, although the interval between them was only a few weeks.

We have found 10 cases reported in which the pregnant woman was treated (Hood, 1961; Sepp and Roy, 1963; LeGouguec *et al.*, 1971) and the diagnosis was proved by blood culture. A wide variety of antibiotics was used—such as penicillin, tetracycline, spiramycin, sulphonamide, chloramphenicol, and streptomycin, alone or in various combinations. These 10 cases resulted in 7 healthy babies, 2 infected babies, and one abortion. Our Case 2 appears to be the first to be described in Britain. Kanamycin and ampicillin in combination proved very effective in the New Zealand outbreak (Becroft *et al.*, 1971) and gentamicin and ampicillin in combination were successful in our patients.

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Water intoxication by the oral route in an infant

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SUMMARY Symptomatic water intoxication is common when hypo-osmolar fluids are given therapeutically, usually intravenously, but it is rare after drinking voluntarily (Wynn and Rob, 1954). We report a case of water intoxication caused by voluntary drinking in an infant.

Case report

A 10-month-old girl was admitted to hospital because of generalised convulsions which had begun an hour earlier. The child was born to a healthy mother after an uneventful pregnancy and normal delivery. Her birthweight was 3200 g and development until admission had been normal. Family history was negative and no history of excessive water requirement was noted.

On the evening before admission she developed a fever (38°C) and slight diarrhoea. The parents were advised by a doctor 'to give her a lot to drink'. The child was restless and between 01.30 and 04.00 hours she drank about 1 litre of water, without the addition of salt or sugar. Soon after 04.00 hours convulsions began. The child was brought to the emergency room. She received diazepam 2 mg IV, but after 10 minutes the convulsions recurred.

Examination on admission showed a well nourished girl weighing 9600 g. The temperature was 38°C, blood pressure 110/70 mmHg, pulse 100/min. She was lethargic and responded only to painful stimuli. Periorbital oedema was noticed.

CSF was clear with no cells, protein 20 mg/100 ml (0·2 g/l), glucose 120 mg/100 ml (6·66 mmol/l), bacterial culture—negative. Serum sugar 315 mg/100 ml (17·5 mmol/l), Ca 9 mg/100 ml (2·25 mmol/l), P 6 mg/100 ml (1·9 mmol/l), urea 25 mg/100 ml (4·15 mmol/l), K 4·3 mEq/l, Na 118 mEq/l (on repeated examination), Cl 82 mEq/l, bicarbonate 25 mEq/l. Urine electrolytes Na 25 mEq/l, K 14 mEq/l. Blood osmolality 255 mmol (normal 280 mmol). Urine osmolality 87 mmol. EEG showed generalised slowing.

She was treated with hypertonic saline (2%) 300 ml IV and after some hours she became alert and began to eat normally; the convulsions did not recur. Serum Na, 8 hours after admission was 138 mmol/l and remained normal thereafter. Her weight the next day was 9050 g; she had therefore lost 550 g. The blood glucose rapidly returned to normal with a 2 hour-postprandial value of 85 mg/100 ml (4·7 mmol/l). EEG returned to normal after a week. She was discharged and at follow-up 6 months later was doing well.

The history, laboratory data, weight loss, and clinical course left no doubt that the diagnosis was one of water intoxication.

Discussion

Involuntary water intoxication can be caused by IV administration of fluids which contain small amounts of saline. It may also follow gastric lavages or enemas, and be present in patients suffering from compulsive water drinking. Voluntary water intoxication in children is rare, and only 5 similar cases have been reported (Dugan and Holliday, 1967; Nickman *et al.*, 1968; Pickering and Hugan, 1971; Crumpacker and Kriel, 1973).

The two principal variables in maximum water tolerance (Pickering and Hugan, 1971) are the ability of the kidney to dilute, and the maximum renal tubular excretion capacity of water. The kidneys in a 3-month infant are mature as regards their ability to excrete water (Fisher *et al.*, 1963) and our 10-month-old patient could therefore be expected to excrete water as satisfactorily as an adult. When a water load is given (20 ml/kg) the expected response would be excretion of at least 75% of the water in 4 hours (De Wardener, 1973), but if the load were more than five times greater, as in our case (110 ml/kg), it is reasonable to expect that such a load would not be excreted and that water intoxication would develop.

One hypothesis for the mechanism of this syndrome is that the infant has an inappropriate secretion of antidiuretic hormone or a delayed switch-off of ADH release. This would lead to retained fluid or a delayed excretion of the water load. As most infants are 'sick' before they are given large, 'voluntary' loads of fluid, one might suggest such a mechanism. Measurements of ADH secretion have not been made in such infants, but the low osmolality of the urine in our patient is against such an hypothesis because, if secretion of ADH is inappropriate, urine osmolality must be high. The hyperglycaemia in our patient may have been caused by the convulsions (Rutter and Smales, 1977).

Symptoms of hyponatraemia usually begin when serum Na <120 mEq/l (Wynn and Rob, 1954), but they will begin sooner if the hyponatraemia develops rapidly, as in our child who probably became hyponatraemic in less than 4 hours.

When treating with hypertonic saline, it is not known how rapidly levels of plasma Na can safely be raised in patients with acute hyponatraemia, nor how long it takes for acute hyponatraemia to cause permanent brain damage. Apart from hypertonic saline (usually 3%) and water restriction, no other form of treatment has proved to be effective (Crumpacker and Kriel, 1973).

This case once more emphasises the need for clarity when prescribing; the laconic order 'to give a lot to drink' allows room for much ambiguity. The physician should be specific with regard to the kind of fluid to be given, its amount, and frequency of administration.

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Copper deficiency in a low birthweight infant

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SUMMARY Copper deficiency is reported in an infant of very low birthweight. It was characterised by extensive bone changes, severe neutropenia, and hypocupraemia. These manifestations could have been missed but for an intercurrent pneumonia which led to an *x*-ray of the chest.

Low birthweight infants go into negative nitrogen balance from birth and there may also be substantial losses of trace elements (Shaw, 1973). Absorption of nutrients may also be poor. It is surprising, therefore, that there have been so few reports of copper deficiency in low birthweight infants (Al-Rashid and Spangler, 1971; Griscom *et al.*, 1971; Ashkenazi *et al.*, 1973; Sann *et al.*, 1978) and it is possible that some cases go unrecognised.

Case report

A Chinese baby, son of a 28-year unmarried hostess at a dance hall, was born spontaneously in the hospital casualty department at 28 weeks' gestation on 24 August 1977. Birthweight 970 g; length 39 cm; head circumference 26 cm. The clinical and radiological features of idiopathic RDS rapidly developed. The infant was nursed in an incubator in 60% O_2, an umbilical artery was catheterised for blood–gas studies, and IV 10% dextrose was given at a rate of 3 ml/hour. Apnoeic attacks necessitated the use of CPAP on 25 August and IV aminophylline was given 1·5 mg six-hourly. Pa_{O_2} varied between 47 and 115 mmHg (6·2 and 15·3 kPa). Metabolic acidosis was corrected with sodium bicarbonate. Parenteral feeding with Aminofusin, dextrose, and Intralipid was started on 26 August. CPAP was stopped on 30 August, and the ambient O_2 concentration gradually reduced. An attempt at nasogastric feeding on 31 August produced blood from the gastric aspirate and Hb fell to 10 g/dl, and then rose to 15 g/dl after a transfusion of 25 ml fresh blood. Parenteral feeding was discontinued on 20 September when the infant's full caloric requirements were being given in the form of Nan (Nestlé) by nasogastric tube. Hb was 11·5 g/dl. On 1 October proprietary ferrous sulphate and multivitamin preparations were started orally. However, on 4 October Hb was 7·6 g/dl; WBC 45·1 × 10^9/l; neutrophils 31%; lymphocytes 69%; platelets 645 × 10^9/l; reticulocytes 4·8%. Films showed 12 nucleated RBC/100 WBC. On the suspicion of vitamin E deficiency (Willoughby, 1977) IM tocopherol 100 mg daily was given for 4 days. Unfortunately, the infant developed bronchopneumonia (treated with IV gentamicin and ampicillin) and on 17 October Hb was 6·3 g/dl; reticulocytes 8·7%. A further 4-day course of tocopherol was given and on 10 November Hb was 11·3 g/dl; reticulocytes 2·6%. The infant was discharged home on 22 November on Nan 75 ml three-hourly × 8, plus iron and vitamin supplements. Weight 2·33 kg; head circumference 32·5 cm.

The baby was readmitted on 13 December extremely ill and convulsing with bronchopneumonia. Weight 3·0 kg. Respirations 60/min. Blood pH 7·03; Pa_{O_2} 73 mmHg (9·7 kPa); Pa_{CO_2} 94 mmHg (12·5 kPa); base excess—7·5 mmol/l. Serum Na 132 mmol/l; K 5·8 mmol/l; Ca 2·4 mmol/l (9·6 mg/100 ml); P 2·38 mmol/l (7·4 mg/100 ml); Mg 1·0 mmol/l (2·4 mg/100 ml). Hb 10·2 g/dl; WBC 20·3 × 10^9/l; neutrophils 26%; lymphocytes 67%; monocytes 7%; reticulocytes 4·6%. CSF normal. There was a good response to cephradine given IV combined with nursing in 40% O_2. However, a repeat chest *x*-ray on 21 December showed widening of the anterior rib ends, subperiosteal reaction, and fractures of the right 6th, 7th, and 8th ribs and of the left 5th, 6th, 7th, and 8th ribs.

A skeletal survey showed diaphyseal subperiosteal new bone formation with cupping and flaring of the metaphyses and severe osteoporosis. There were fractures of the lower ends of the left radius and right ulna (Figure). Repeat blood tests showed serum Ca 2·1 mmol/l (8·4 mg/100 ml); P 2·94 mmol/l (9·1 mg/100 ml); alkaline phosphatase 610 μmol/min per litre (Chinese adults 35–115). VDRL negative. On 19 January 1978 serum Cu was 0·7 μmol/l (4·5 mg/100 ml) (normal 11–25), and serum caeruloplasmin was barely detectable (normal 62–108 μmol/min per litre). Hb was 11·9 g/dl; WBC 7·3 × 10^9/l; neutrophils 1%; lymphocytes 90%; monocytes 8%; eosinophils 1%; serum Fe 8 μmol/l (44·7 μg/100 ml); TIBC 51 μmol/l (285 μg/100 ml). On 25 February, when the infant had been on cereals in addition to the milk formula for 52 days, serum Cu was 2·0 μmol/l (12·7 μg/100 ml); caeruloplasmin 10 μmol/min per litre; plasma ascorbate 94·2 μmol/l (1·6 mg/100 ml); serum zinc 9·2 μmol/l (60·1 μg/100 ml) (Chinese adult range 15·7 ± 2·75 μmol/l). *X*-rays taken on 1 March already showed early healing of bone lesions but the infant was started on 0·6 ml of 0·5% copper sulphate solution daily. On 14 March serum Cu was 10 μmol/l (63·7 μg/100 ml); caeruloplasmin 43 μmol/min per litre. Hb was 12·4 g/dl; WBC 15·6 × 10^9/l; neutrophils 47%; lymphocytes 51%; monocytes 1%; eosinophils 1%; reticulocytes 2·6%; platelets 339 × 10^9/l. Copper supplements were stopped on 22 March when serum Cu was 22 μmol/l (140 μg/100 ml); caeruloplasmin 65 μmol/ min per litre. *X*-ray on 29 March showed almost complete healing of bone lesions apart from residual subperiosteal reaction in both femora, although bone-age was only 3 months. The infant went home on 18 May, weight 4·8 kg, on feeds of Cow and Gate Babymilk Plus and mixed feeding. He was still unable to sit unsupported or to roll over from the supine to the prone posture, but in the prone position he could lift his head and chest off the table and he made attempts to grasp objects. Unfortunately his home environment is unlikely to encourage much stimulation.

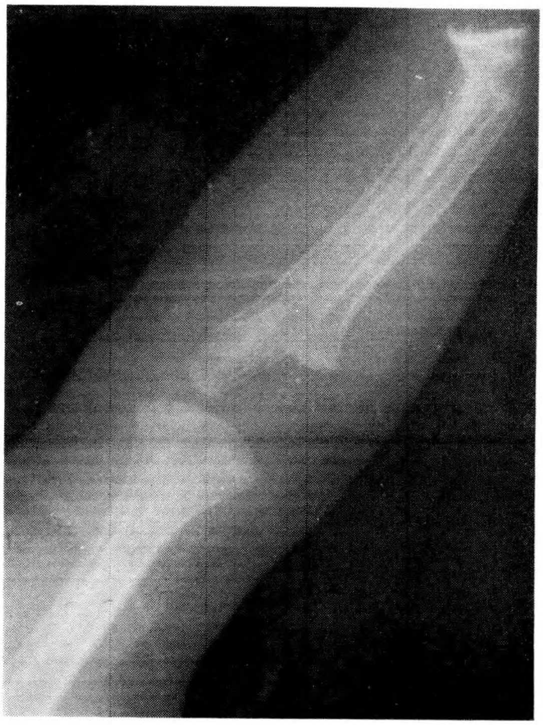

Figure *X-ray at age 4 months showing subperiosteal reaction, osteoporosis, flaring and cupping of metaphyses, and fracture of lower end of radius.*

Discussion

The diagnosis of copper deficiency in this case is based upon the characteristic bone changes, severe neutropenia, and extremely low serum copper and caeruloplasmin levels. Anaemia is common in copper deficiency but was absent in our patient. When the bone changes were first discovered our initial suspicion was rickets. Indeed, this has been reported in association with copper deficiency in a low birthweight infant (Sann *et al.*, 1978). However, the high serum phosphate level made this diagnosis unlikely, particularly as the infant had been receiving a calculated daily intake of at least 10 μg vitamin D. We have not seen such severe subperiosteal new bone formation in rickets but measurements of plasma 25-OHD$_3$ or iPTH were not available to us. There was no evidence of nonaccidental injury and the long bone changes were incompatible with this diagnosis. If this infant had not been readmitted to hospital with pneumonia the diagnosis would have been missed because even after finding extensive bone changes on *x*-rays there was no clinically obvious beading of the ribs or epiphyseal enlargement, and it is probable that spontaneous healing would have followed the introduction of mixed feeding. On the other hand, a neutropenia of 1% must have greatly reduced the infant's resistance to infection.

Copper deficiency has been reported in older infants after prolonged total parenteral nutrition (Karpel and Peden, 1972; Heller *et al.*, 1978) as well as in very low birthweight infants. In our patient parenteral nutrition was only total for 6 out of 26 days, and the extreme prematurity and low birthweight were likely to be more important factors leading to copper deficiency.

We thank Dr L. Y. Y. Fong for the serum zinc analysis.

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Pulmonary candidiasis in cystic fibrosis

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SUMMARY A child with cystic fibrosis and asthma developed pulmonary candidiasis. Predisposing factors in this patient were prolonged antibiotic therapy, high-dose corticosteroids, and intravenous catherisation. A diagnosis was made by lung puncture and confirmed by rapid response to 5-fluorocytosine.

Pulmonary candidiasis is an invasion of viable lung tissue by *Candida* species. It has long been known that this occurs in patients with impaired host resistance—such as those with Hodgkin's disease or leukaemia, and those on cytotoxic therapy. In 1844 Bennett commented: 'it is indicative of great depression of the vital powers and impairment of the nutritive functions of the economy' (Winner and Hurley, 1966).

Candida colonisation is seen in the tracheobronchial tree of children with cystic fibrosis on long-term antibiotics. Pulmonary candidiasis, however, has not been reported in such children.

This is a report of a child with cystic fibrosis and asthma requiring corticosteroids, who developed pulmonary candidiasis and responded to treatment with 5-fluorocytosine.

Case report

A 6½-year-old girl had cystic fibrosis diagnosed in the first year of life and associated bronchial asthma. She was initially well maintained on standard antibiotic and physical therapy for cystic fibrosis lung disease, with intermittent bronchodilator treatment for the asthma.

At age 5 years she required continuous bronchodilators and, subsequently, three intermittent courses of corticosteroids to control the wheeze. At 6 years more prolonged courses of high-dose prednisolone were necessary to control quite severe airways obstruction but these were reduced to a maintenance dose of 4 mg daily. During a course of high-dose prednisolone for an acute exacerbation of airways obstruction she became increasingly lethargic, lost weight, and developed a fever which reached 39°C daily. She developed rapid shallow breathing with fine inspiratory crepitations. Chest *x*-rays showed increased reticulonodular markings (Figure).

Intravenous cloxacillin and gentamicin, and later chloramphenicol and carbenicillin, were given for nearly 4 weeks without response. On several occasions sputum cultures grew *Escherichia coli*, *Streptococcus* species, *Haemophilus influenzae*, and *Achromobacter* species, but moderate to profuse growth of *Candida* species, not *C. albicans*, was always present. Multiple blood cultures were negative. Immune function tests were normal. Tuberculosis, autoimmune disease, and sepsis elsewhere were excluded.

A lung puncture was performed with instillation of 2 ml saline into the lung and aspiration of alveolar fluid. This fluid was smeared and cultured. A pure growth of *Candida* species, not *C. albicans*, was obtained.

She was started on 5-flurocytosine orally; within

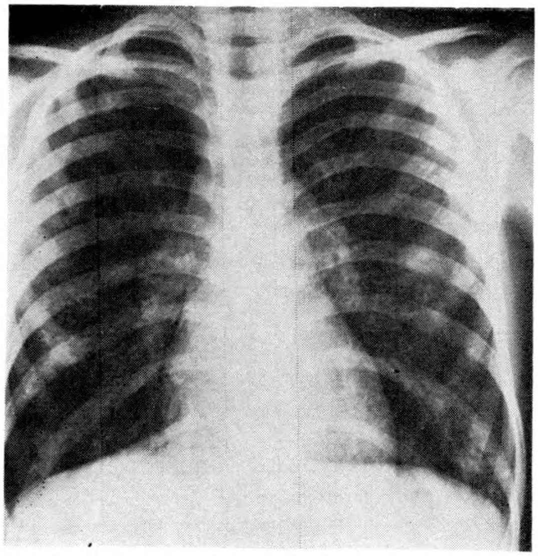

Figure *Chest x-ray at the onset of the febrile illness. The lungs are overinflated. There is patchy nodular consolidation throughout both lung fields with prominent peripheral parenchymal opacities. The hilar vessels are prominent.*

4 days her condition had improved, her appetite had returned, and she became ambulant for the first time in 2 months. She was afebrile within 10 days. Chest *x*-ray one month later showed significant clearing. 5-Fluorocytosine was continued for 6 weeks. She developed mild diarrhoea during the last week of this regimen.

Discussion

The rarity of pulmonary candidiasis is attributed to a natural resistance of columnar epithelium to invasion by the *Candida*, which is particularly prone to attack stratified epithelium. Pulmonary candidiasis occurs when there are impaired host defence mechanisms. It has been known to present as severe tracheobronchitis, bronchopneumonia, or pulmonary abcess. Although not usually seen in cystic fibrosis, predisposing factors in this child were a debilitating disease, prolonged antibiotic and corticosteroid therapy, and prolonged intravenous catheterisation (Hurley *et al.*, 1975).

Establishing a diagnosis can be difficult as was shown in this child. The clinical findings of tachypnoea and fever, with crepitations and rhonchi in the chest, are nonspecific and the radiological findings are not characteristic (Goldstein and Hoeprich, 1972). Candidaemia may not be associated with tissue invasion and, on the other hand, a negative blood culture does not exclude invasive candidiasis (Mirsky and Cuttner, 1972). Sputum culture does not indicate invasion. The most reliable method of diagnosis is demonstration of the fungus in lung tissue histologically. Lung puncture is next best, but even so, *Candida* can be cultured from lung fluid without invasion (Klein, 1969; Bandt *et al.*, 1972).

Treatment of pulmonary candidiasis with 5-fluorocytosine appears to be effective (Kohlschütter and Pelet, 1974), There are few side effects with this drug, those described being predominantly anorexia, nausea, vomiting, and diarrhoea. There have been some reports of haemopoietic depression as well as renal and hepatic toxicity. *Candida* has been noted to develop resistance to 5-fluorocytosine. Amphotericin B has also been used for the treatment of candidiasis but it was not used in this instance because of its known toxicity. The combination of these two drugs in extremely ill patients has been recommended (Montgomerie *et al.*, 1975).

Pulmonary candidiasis, although a rare complication, should be considered in children with cystic fibrosis who develop a febrile illness not responding to antibiotics. This complication may become an increasing problem with the use of corticosteroids and long-term intravenous catheters in a small group of children with cystic fibrosis in whom this type of treatment appears warranted.

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Effective treatment for rhinopulmonary mucormycosis in a boy with leukaemia

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SUMMARY Lymphoblastic leukaemia in a 3-year-old child was complicated by rhinopulmonary mucormycosis. This was successfully treated by surgical resection of the nasal mass, pulmonary lobectomy, combined with amphotericin.

Effective treatment of childhood lymphoblastic leukaemia has been associated with an increased incidence of atypical infections (Hughes, 1971; Krick and Remington, 1976), including phycomycosis (Harris, 1955; Mirsky and Cuttner, 1972; Myer *et al.*, 1972). Successful management of rhinopulmonary mucormycosis in childhood malignancy has not been reported.

Case history

In July 1971, a 3½-year-old white boy with a leucocyte count of 7·7 × 10^9/l was diagnosed as having acute lymphoblastic leukaemia (ALL). Chemotherapy was begun with daily prednisolone (40 mg/m^2) and weekly vincristine (1·5 mg/m^2). Once in remission at 4 weeks, central nervous system prophylaxis was given (2000 rads to the craniospinal axis over 13 days with weekly injections × 2 of intrathecal methotrexate 0·5 mg/kg). Maintenance was with daily 6-mercaptopurine (50 mg/m^2), weekly oral methotrexate (20 mg/m^2), and cyclophosphamide (200 mg/m^2), with vincristine and prednisolone pulses every 3 months.

In May 1974 the child developed a right hemiparesis and a left 3rd and right 6th and 7th cranial nerve palsies. Fundoscopy was normal and there was no meningismus. Investigations identified a 2–3 cm mass to the left of the midline at midbrain level, deviating the 3rd ventricle to the right. Lumbar thecal pressure was normal with CSF glucose 65 mg/100 ml (3·6 mmol/l) and protein 38 mg/100 ml (0·38 g/l), with no cells. Abnormal vascularity was confirmed on carotid arteriography. Biopsy was deferred because of the lesion site but a trial of irradiation to a total dose of 4000 rads (2500 rads to whole brain and 1500 rads to midbrain) over 18 days produced slight improvement in limb power only. This was considered to suggest a new tumour, not a leukaemic or encephalopathic lesion. Computerised axial tomography (CAT) showed an increase in tumour size.

Leukaemic therapy was stopped and oral 1–(2-chloroethyl)–3 cyclohexyl–1 nitroso–urea (CCNU) began (100 mg/m^2) orally every 6 weeks. Between the first two dosages the tumour enlarged by a further 20% with neovascularity, but the child remained clinically well at school. Neither bone marrow nor CSF showed evidence of leukaemic relapse until April 1976 (22 months after stopping antileukaemic treatment) when he developed a left-sided bronchopneumonia coincident with haematological relapse. Leukaemic therapy was restarted and CCNU stopped. Remission was again achieved after one month. CAT scan showed calcification without further enlargement of the midbrain lesion. One month later (2 years after the development of hemiparesis) he had fever and mucopurulent nasal discharge, with bilateral opacified ethmoid and maxillary sinuses, left lower lobe pulmonary infiltrates, and the left hemidiaphragm was raised. *Staphylococcus aureus* was initially cultured from the nose but the condition did not improve with treatment on methicillin. Nasal debridement showed a large necrotic polypoid mass containing irregular broad fungal hyphae, mostly nonseptated, suggestive of mucormycosis (Fig. 1). Cultures were negative. The mass had occupied the nares, right maxillary antrum, and ethmoid sinus, causing septal perforation. After a test dose (1 mg), amphotericin in a dose of 0·25 mg/kg per day was begun and increased by 0·25 mg/kg per day to a maximum dose of 1 mg/kg per day. Each dose was given in 250 ml 5% dextrose with 250 units heparin and 25 mg hydrocortisone over 6 hours. Periodically, raised blood urea, nitrogen, and creatinine levels necessitated dosage being interrupted for a maximum of 2 days. Altogether 1212 mg was administered over 7 weeks. The nose progressively improved but despite intensive physiotherapy the lung infiltration worsened (Fig. 2). Needle aspiration, bronchoscopy, and left lower lobectomy followed. On each occasion necrotic material containing occasional branching nonseptated hyphae was obtained. All fungal cultures however were negative. Postoperative recovery was complicated by wound haematomata but no infection. No further amphotericin was given.

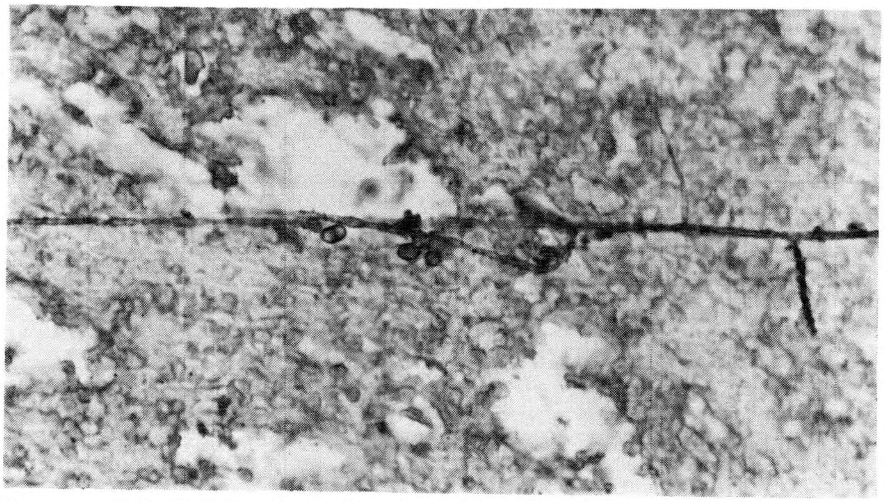

Fig. 1 *Fungal hyphae identified in debris from the nares.*

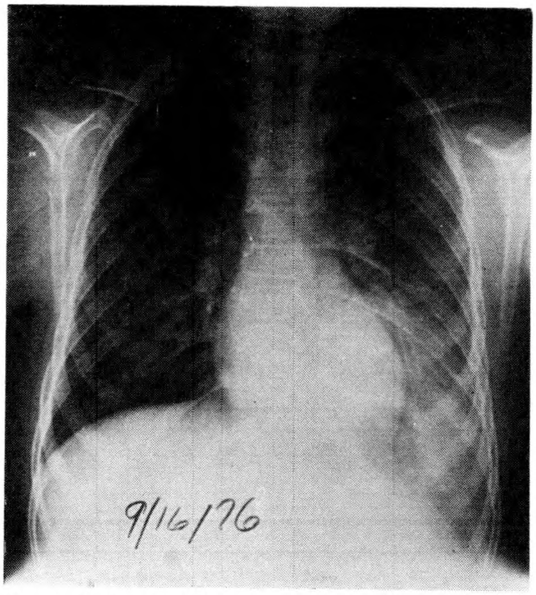

Fig. 2 *Left lower lobe pneumonic consolidation.*

To date (2 years 7 months after diagnosis of rhinopulmonary mucormycosis) the child remains well on antileukaemic chemotherapy in complete remission, but he has a persistent thalamic tumour showing contrast enhancement but no increase in size. He has no rhinorrhoea or evidence of active pulmonary disease despite a persistently paralysed left hemidiaphragm and a right hemiparesis. He attends school regularly and plays football.

Discussion

Nearly 3 years after the diagnosis of leukaemia this boy developed an intracerebral lesion and after 2 further years rhinopulmonary mucormycosis. That these two occurrences were related had to be considered. He has shown no CNS symptom progression while investigations gave no evidence of meningeal disease but showed neovascularity with late calcification. Without histology the exact nature of the mass is uncertain. Retrospectively, we have to consider rhinocerebral mucormycosis which can occur in children (Harris, 1955; McBride *et al.*, 1960; Baker, 1962). The usual features of systemic infection of ophthalmoplegia, uncontrolled diabetes insipidus, and meningoencephalitis were all absent (Harris, 1955; McBride *et al.*, 1960). Rapidly fatal isolated cerebral mucormycosis has been reported (Myer *et al.*, 1972). Our patient had the lesion for at least 2 years without antifungal therapy but with continuing chemotherapy. Mucormycosis is a very aggressive infection and if untreated it will progress to death within a matter of weeks (Harris, 1955; McBride *et al.*, 1960). Mucor hyphae were seen in nasal and lung tissue. The incidence of mycotic infections in leukaemic patients has progressively risen and now up to 30% of significant infections are of such a nature (Mirsky and Cuttner, 1972; Myer *et al.*, 1972; Krick and Remington, 1976). Aspergillus and the phycomycetes are also showing a differential increase compared with Candida (Mirsky and Cuttner, 1972; Myer *et al.*, 1972; Krick and Remington, 1976).

Phycomycosis normally originates in the nose and paranasal sinuses and characteristically invades the walls and lumen of blood vessels. In leukaemic patients it usually also invades lung and sometimes becomes disseminated (Mirsky and Cuttner, 1972; Myer *et al.*, 1972). Any lung lobe can be affected and infarction is common (Medoff and Kobayashi, 1972). The organism is difficult to recover and grow in culture. Frequently the diagnosis is made at necropsy (Krick and Remington, 1976). It is not a common human saprophyte and therefore the presence of mucor hyphae on any biopsy smear must be taken as strong evidence of infection (Myer *et al.*, 1972; Krick and Remington, 1976). This is especially so in a febrile leukaemic patient with a persistent and/or progressive antibiotic resistant pneumonia.

Our patient is thought to be the first child with leukaemia to be successfully treated with amphotericin and surgical resection for extensive rhinopulmonary mucormycosis. We stress the need for aggressive diagnostic procedures, including debridement and resection, in conjunction with adequate amphotericin if this diagnosis is suspected.

We acknowledge the help of Dr A. Yeager and Dr T. Long in preparing this manuscript.

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Neonatal aspergillosis accompanying fulminant necrotising enterocolitis

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SUMMARY A preterm infant developed fulminant necrotising enterocolitis, subsequently resulting in death. Necropsy examination showed diffuse aspergillosis. Reports are reviewed, and possible mechanisms resulting in *Aspergillus* infection in this infant are discussed.

Disseminated aspergillosis in all age groups is almost always associated with an underlying chronic illness or other predisposing factors—such as prolonged administration of antibiotics or corticosteroids (Zimmerman, 1955; Luke *et al.*, 1963; Riley, 1972). The *Aspergillus* is a fungus which rarely causes disease in humans. In children, particularly during the neonatal period, aspergillosis is exceedingly rare (Allan and Andersen, 1960; Luke *et al.*, 1963). We recently unexpectedly discovered diffuse aspergillosis in a preterm infant dying from fulminant necrotising enterocolitis (NEC). We can find only five reports (see Table) of neonatal aspergillosis (Zimmerman, 1955; Akkoyunlu and Yucel, 1957; Allan and Andersen, 1960; Matturri and Fasolis, 1962; Luke *et al.*, 1963). We can find no previous report of this organism in association with NEC. Accordingly we describe our findings.

Case report

A 950-g boy was born by caesarean section to a 25-year-old primigravid mother after 31 weeks' gestation. Membranes ruptured spontaneously 32 days before delivery. The mother was observed in the hospital for 4 days and discharged home to rest in bed. She was readmitted 2 weeks before delivery because of peptic ulcer disease. She was treated with diazepam, diphenoxylate-hydrochloride with atropine sulphate, trimethobenzamide hydrochloride, acetaminophen, chlordiazepoxide hydrochloride with clidinium bromide, and various antacids. In addition she was given vitamins, secobarbital sodium, diphenhydramine hydrochloride, and iron dextran injection. A cholecystogram was normal. A lecithin/sphinogomyelin (L/S) ratio on amniotic

Table *Reported cases of generalised aspergillosis in neonatal period*

Author	*Year reported*	*Age at diagnosis (days)*	*Distribution of organism*	*Method of diagnosis*	*Predisposing factor(s)*
Zimmerman	1955	30	Lungs, brain, liver	Culture, necropsy sections	Staph sepsis, antibiotics, corticosteroids
Akkoyunlu and Yucel	1957	20	Lungs, meninges	Culture	Antibiotics
Allan and Andersen	1960	18	Lungs, liver, heart, spleen, kidneys, bowel	Culture, necropsy sections	?None
Matturri and Fasolis	1962	37	Heart, lungs, thymus, kidneys, subcutaneous tissue	Necropsy sections	Anal atresia, antibiotics
Luke *et al.*	1963	51*	Heart, kidneys, brain, blood	Culture, necropsy sections	Hydrops fetalis, *Escherichia coli* sepsis, antibiotics, chronic inanition
Present report	1978	16	Lungs, liver, bowel	Culture, necropsy sections	Prematurity, necrotising enterocolitis, antibiotics

*Infection related to neonatal problem; infant never left hospital after birth.

fluid collected vaginally 10 days before delivery was 2·3/1. Vaginal bleeding and vague uterine contractions developed 2 days before delivery. Ultrasound examination was unrevealing. Several hours before delivery the maternal temperature rose to 37·5°C, associated with increasing abdominal pain and increase in fetal heart rate. In view of the mature L/S ratio and increasing hazard of infection to mother and fetus, a primary caesarean section was performed under general anaesthesia. Oligohydramnios was noted at delivery. Apgar scores were 7 at one and five minutes. The infant was taken to the high-risk nursery, pink and crying, with mild retractions. Examination of the placenta showed massive subchorionic fibrin deposition.

Physical examination showed a preterm infant who was pink, active, and responsive, with no respiratory distress. The head appeared disproportionately large for the body. Air exchange was fair bilaterally. The skin was dry and peeling, with diminished subcutaneous tissue. Neurological examination showed a fairly good cry and suck, normal tone, and no reaction to Moro's test.

The infant was given maintenance fluids by peripheral vein. Cultures of peripheral blood, urine, and stool were subsequently reported to be negative. At 10 hours nasogastric feedings were started. The first 6 days of life were relatively uneventful, and the infant tolerated gradual formula increases well. On day 7 he developed lethargy, abdominal distention, absent bowel sounds, poor feeding, increasing gastric residue, and grossly bloody stools. Roentgenograms showed evidence of pneumatosis coli. Repeat cultures were taken of blood, urine, and CSF, and ampicillin and gentamicin were started. Feedings were stopped, and nasogastric suctioning was initiated. All repeat cultures were again negative. Frequent serial abdominal *x*-rays showed no change. However, the condition of the infant continued to deteriorate, with bloody stools and progressive apnoea and bradycardia requiring frequent vigorous stimulation. On day 9 he became cyanotic and unresponsive, requiring intubation and respiratory assistance.

On day 13 an upright roentgenogram of the abdomen showed free air under the diaphragm. Platelet count was 3·0 × 10^9/l, and partial thromboplastin time and prothrombin time were prolonged. Heparin and platelets were given. Exploratory laparotomy showed a recent perforation of the caecum; about 150 ml of serosanguineous fluid was obtained during surgery. Because of the moribund condition of the patient, a loop ileostomy was placed. Cultures of peritoneal fluid subsequently showed an unidentified anaerobe. Accordingly, clindamycin was started, and ampicillin was stopped.

After surgery the infant developed renal failure, followed shortly by rising serum potassium levels. Blood glucose became very labile, ranging from 11 to 1011 mg/100 ml (0·6 to 0·056 mmol/l). On the last day of life, he developed arrhythmias compatible with hyperkalaemia. His condition gradually deteriorated and he died on day 16. Multiple necropsy cultures showed no growth in cardiac blood or CSF, nor was there growth in either lung or in the tip of endotracheal tube. *Clostridium* species was recovered from rectum, ileostomy site, and peritoneal fluid; *Aspergillus* was recovered from the ileostomy site and peritoneal fluid.

Necropsy findings

Gross description. There were extensive areas of ecchymoses with superficial ulcers. The abdominal cavity contained a scanty amount of dark red fluid. The intestinal loops were distended and dark purple. There was an area of perforation at the base of the appendix; two areas of perforation were present in the descending colon. The liver was enlarged, extending 4 cm below the right costal margin. There were large erosions of the mucosa of the stomach. The brain showed extensive subarachnoid haemorrhage of the left temporal lobe and cerebellum.

Microscopical description (Figs 1 and 2). There was diffuse necrosis of the wall of the small intestine and colon with abundant colonies of *Aspergillus* infiltrating the wall. Similar findings were observed at the site of the gastric erosions. There was a diffuse bronchopneumonia with extensive infiltrates of *Aspergillus*. The liver showed areas of necrosis with abundant colonies of *Aspergillus*.

Discussion

Neonatal NEC has been described in detail (Pochaczevsky and Kassner, 1971; Stevenson *et al.*, 1971; Frantz *et al.*, 1975). Bacterial infection with resultant peritonitis and septicaemia is a recognised complication of the disease (Hopkins *et al.*, 1970). Infection caused by bacteria or viruses has been considered as one of the aetiological factors, although one report did not give any bacterial, viral, or fungal cause of NEC (Virnig and Reynolds, 1974). Levin and Isaacson (1960) reported a preterm infant who died on day 12 of NEC with resultant perforation and peritonitis; necropsy examination showed fungal hyphae within bowel lumen, wall, and serosa near the site of perforation. Although cultures were not taken, the appearance of the organism was thought to be consistent with mucormycosis. We can find no other report that indicates an association between fungal infection and NEC.

The *Aspergillus* species is common and rarely causes disease in humans. The organism may be encountered as a contaminant of laboratory cultures. The presence of *Aspergillus* in multiple sites in this infant—for example stomach, small intestine, liver, and lungs—is strong evidence against laboratory contamination. The patient reported here had a fulminant variety of NEC, with many severe complications (intestinal perforation, peritonitis, possible anaerobic sepsis, disseminated intravascular coagulation, renal failure). This overwhelming form of NEC in association with prematurity possibly compromised him immunologically. The *Aspergillus* organism is a known 'opportunist'; the chronically ill condition of this preterm infant in association with a severely compromised gastrointestinal tract and broad-spectrum antibiotic therapy resulted in

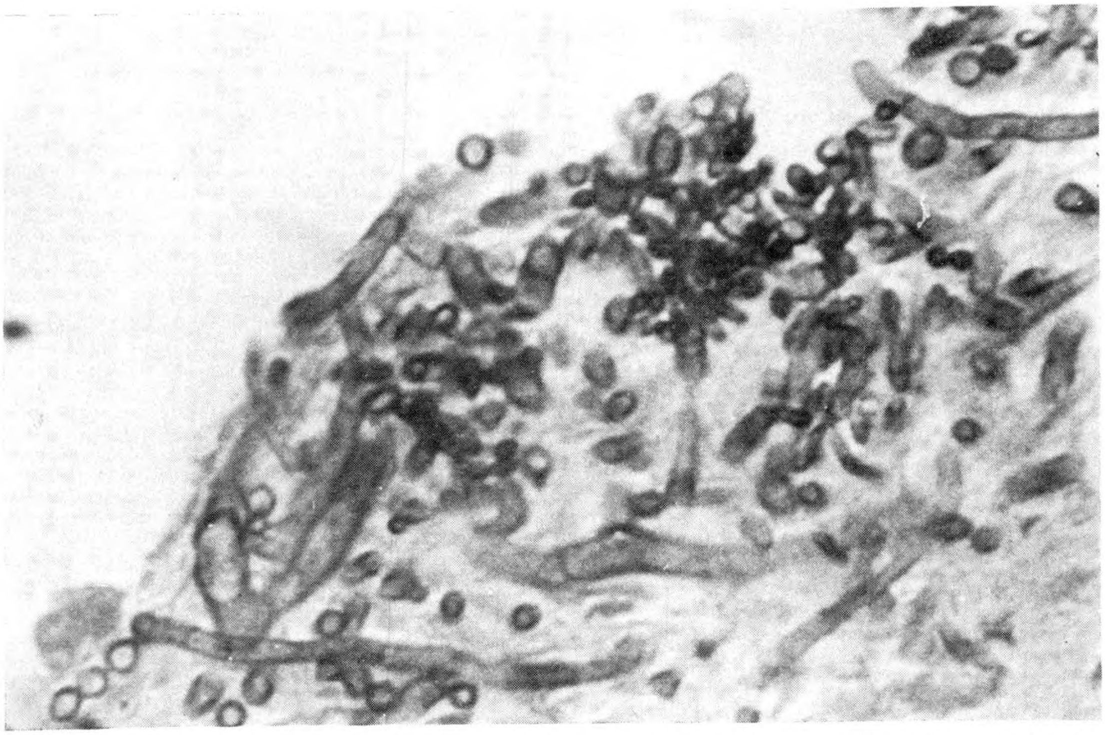

Fig. 1 *Section of the ulcerated mucosa of small intestine with abundant growth of Aspergillus. (Haematoxylin and eosin, ×400).*

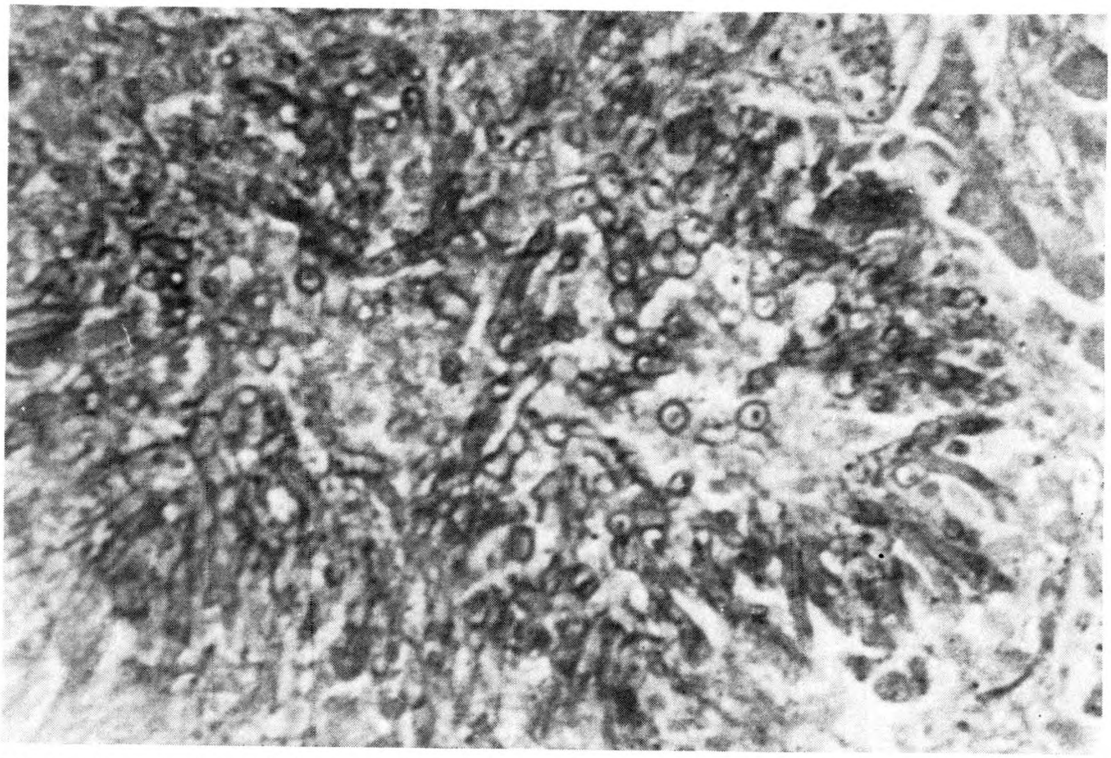

Fig. 2 *Mass of hyphae in the liver parenchyma with extensive necrosis of liver cells. (Haematoxylin and eosin, ×400).*

an ideal environment for *Aspergillus*. The fungus probably invaded the wall of the ulcerated stomach and necrotic intestine, extending via the portal circulation to the liver and subsequently via the blood stream to the lungs.

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Archives of Disease in Childhood, 1979, **54**, 563–567

Correspondence

Simple method for stabilising umbilical catheters

Sir,

We were interested in the letter from Gatrad (*Archives*, 1979, **54**, 166). For the last 2 years we have used a method for stabilising umbilical catheters that has almost eliminated the problem of accidental dislodgement.

The umbilical cord is cut approximately 2 cm from the base, sterilised with povidone-iodine solution, and the lumen of the umbilical artery carefully dilated with fine forceps. A fluid-filled 5 FG catheter is then inserted and advanced in the usual manner. Once positioned, there should be free flow of arterial blood from the catheter. Position of catheter tip at the level of the 3rd or 4th lumbar vertebra is ascertained by *x*-ray. A 4–0 silk purse string suture is passed around the artery containing the catheter (not the entire base of the cord) and tied. One end of this suture is passed through the skin at the base of the cord. This is tied and cut so as to leave about 4–5 cm of free ends of the suture. These lengths of suture are then taped securely to the catheter just above its entry into the artery with standard 2.5 cm adhesive tape. A length of umbilical cord tape is passed around the waist of the infant and tied loosely. This loop is taped securely to the catheter 5–6 cm above the previous piece of tape, thus preventing the catheter from being dislodged should traction be applied to it during *x*-rays, routine care, or weighing of the infant. Povidone-iodine solution is applied twice daily to the cord and to the place at which the catheter is inserted until it is removed. The Figure shows this method of stabilisation in a low birthweight infant.

Techniques of catheterisation of umbilical vessels have been well described. Most methods of stabilisation combine purse string suturing around the catheter with taping of the catheter to the skin of the infant with or without a covering gauze dressing. This can lead to the catheter slipping through the purse string suture and to trauma to large areas of skin in low birthweight infants. Such areas subsequently serve as sites of increased fluid and protein loss and can be potential portals of entry for infection. Even paper tape may denude the skin of the small premature baby during the first 3 days of life.

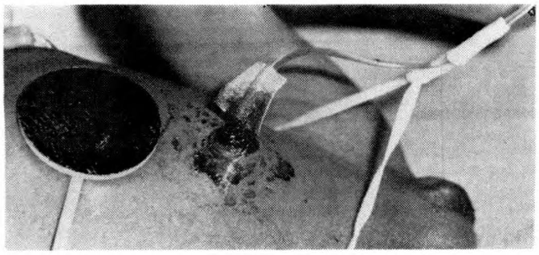

Figure *Method of stabilising umbilical catheter.*

Our technique, besides making accidental dislodgement of the catheter unlikely, additionally allows the umbilical cord to remain dry, and reduces the risk of colonisation with hospital-acquired organisms.

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Chloramphenicol and phenobarbitone —a drug interaction

Sir,

I read with interest the Short Report by Bloxham *et al.* (*Archives*, 1979, **54**, 76). The authors are mistaken in their belief that the interaction between these drugs has not been specifically reported in man. Windorfer and Pringsheim (1977) reported that premature and newborn babies (n = 20) who received phenobarbitone in addition to chloramphenicol and penicillin had lower levels of chloramphenicol than groups of comparable babies who received chloramphenicol alone (n = 29) or chloramphenicol and penicillin combined (n = 35).

The Short Report draws attention to the problem of drug interactions, and two points are worthy of mention. Chloramphenicol is known to inhibit the hepatic microsomal enzyme system (Adams *et al.*, 1977) and it causes a reduction in phenobarbitone clearance (Koup *et al.*, 1978) and raises the levels of phenytoin and other drugs (Christensen and Skovsted, 1969). It would therefore have been particularly interesting to have seen the trend in serial phenobarbitone concentrations in the two cases cited by Bloxham *et al.* Sodium valproate may offer no advantage, as although it appears to have little or no enzyme-inducing properties, it may in fact inhibit the microsomal enzyme system and this is presumably one mechanism by which an increase in phenobarbitone, phenytoin, and primidone concentration occurs when these drugs are used in combination with sodium valproate (Windorfer *et al.*, 1975; Vajda *et al.*, 1976).

It is imperative that all possible drug-drug interactions are considered when contemplating giving a combination of drugs. The importance of drug level monitoring, especially in these circumstances, is worth emphasising.

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Drs Durbin and Winterborn comment:

We are pleased that Dr Rylance agrees with the aim of our report which was to stress the need for regular monitoring of blood levels when chloramphenicol is used in combination with other drugs, particularly enzyme-inducing anticonvulsants. We did not measure serial phenobarbitone levels but neither patient showed evidence of toxicity in the form of unduly prolonged or increasing drowsiness. Any possible advantage of sodium valproate remains to be established by direct observation, but the evidence cited by Dr Rylance suggests that by inhibiting degradation, sodium valproate may actually increase the antibacterial activity of a given dose of chloramphenicol.

We thank Dr Rylance for drawing our attention to the report by Windorfer and Pringsheim (1977) which stated that addition of phenobarbitone to the *combination* (our italics) of chloramphenicol and penicillin reduced the serum chloramphenicol concentration in the neonate but not in infants or older children. We do not agree that their report invalidates our claim to the first specific report of the interaction between chloramphenicol and phenobarbitone in man. Windorfer and Pringsheim used a photometric assay which fails to distinguish between active chloramphenicol and its breakdown products. Their finding of increased chloramphenicol levels in neonates and infants treated with penicillin and chloramphenicol can be attributed at least in part to penicillin-induced renal retention of the breakdown products (Windorfer, 1972). It is therefore difficult to interpret their finding in neonates and infants that serum chloramphenicol concentration did not differ significantly between patients given chloramphenicol alone and those given the combination of chloramphenicol + penicillin + phenobarbitone. In the only group they were able to assess, they found no significant difference in the serum chloramphenicol levels of infants given chloramphenicol alone (n = 45) and of those given chloramphenicol + phenobarbitone (n = 40). The contradiction between their findings and ours may be explained by the relatively insensitive method of their study. They compared single measurements of serum (chloramphenicol + breakdown products) to the weight-related dose of chloramphenicol in children of different ages given different combinations of drugs, without allowing for the earlier duration of treatment. We suggest that Windorfer and Pringsheim would have demonstrated a significant effect of phenobarbitone on the serum level of biologically active chloramphenicol if, as we did, they had used a bioassay to measure the serum levels serially. In the event they did not.

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Henoch-Schönlein syndrome after chickenpox

Sir,

On the basis that one swallow does not make a summer, readers may not have paid too much attention to the letter from Halle (*Archives*, 1979, **54**, 166) suggesting that it was the first account of Henoch-Schönlein syndrome after chickenpox. However, the association has been reported before. In a series of 88 children with Henoch-Schönlein nephritis (Meadow *et al.*, 1972) we found that 5 children had had a specific infectious fever in the 6 weeks preceding onset of purpura. These illnesses were chickenpox in 2 children, and measles, rubella, and scarlatina in the other 3. The onset of chickenpox had been 5 weeks in one child and 10 days in the other before the onset of purpura.

Furthermore Pedersen and Petersen (1975) reported a 2-year-old boy who developed Henoch-Schönlein syndrome 16 days after the onset of chickenpox. Their paper illustrates the difficulty in defining Henoch-Schönlein syndrome. Chickenpox can be followed by a nonthrombocytopenic purpura: it can also be followed by a nephritis. If the two were to happen together and the child also had a tummy ache or an aching joint the diagnostic label would be Henoch-Schönlein syndrome.

As is so often the case in medicine, the more cumbersome the diagnostic label the more likely that it is being used to hide our ignorance of its pathogenesis.

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Slow-release theophylline preparations

Sir,

The study by McKenzie and Baillie (*Archives*, 1978, **53**, 943) indicates the growing appreciation that theophylline has the potential to control the symptoms of chronic asthma when serum levels are maintained at between 10 and 20 μg/ml. As they suggest, sustained-release theophylline formulations offer therapeutic advantage by allowing more stable serum theophylline concentrations; this results in longer intervals between doses than are possible with either cromoglycate or β-agonist bronchodilators. Not all sustained-release theophylline preparations are completely and reliably absorbed, however, and each product differs in its absorption characteristics even when absorption is complete (Weinberger *et al.*, 1978).

The degree to which a theophylline formulation maintains acceptably stable levels relates to both the rate of absorption of the product and the rate of elimination of the individual. As children have average half-lives of elimination of 3·7 hours, slowly absorbed products are particularly important if excessive fluctuations in serum theophylline concentration are to be avoided. The clinical importance of lessening these fluctuations has been shown by the decrease in bronchodilatation (Levy and Koysooko, 1975), and blocking of exercise-induced bronchospasm that is parallel to decreasing serum concentration (Pollock *et al.*, 1977). While McKenzie and Baillie argue for the convenience of 12-hour dosing with the sustained-release preparations, their data (McKenzie and Baillie, 1978) and ours (Weinberger *et al.*, 1978) suggest that 8-hour dosing may often be more appropriate except for the slowest of the reliably and completely absorbed sustained-release preparations or for patients with slow rates of elimination.

The rate of elimination of theophylline also determines dosage (Jenne *et al.*, 1976; Ginchansky and Weinberger, 1977). The problems that can result from the variable dosage requirements for theophylline were illustrated in a study that compared theophylline with cromoglycate (Cromolyn, Intal) performed at the Hammersmith Hospital and at two residential treatment centres for asthma in Denver (Hambleton *et al.*, 1977). Whereas all of the patients in Denver tolerated theophylline, 6 patients at the Hammersmith Hospital did not, and therefore could not enter the study. The difference can be attributed to the manner in which theophylline dosage was determined. Each patient in Denver was given an individual theophylline dose while an 'average' dose, similar to that recommended by McKenzie and Baillie, was initiated in all the Hammersmith Hospital patients. The resulting intolerance in some patients was predictable (Wyatt *et al.*, 1978).

We have found that clinical titration using serum theophylline measurement as a guide gives a high degree of safety and provides the greatest likelihood of efficacy in the management of chronic asthma (Ekwo and Weinberger, 1978; Hendeles *et al.*, 1978).

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Dr McKenzie comments:

We agree with Dr Weinberger that ideally the starting dosage of theophylline should be small, blood levels checked, and dosage built up. However, many of our patients live some distance from the hospital and we feel that it would be impracticable to recall these children frequently to measure levels and adjust dosage. We prefer to titrate our patients by starting with a high dosage, checking levels, and then raising or lowering the dosage as necessary. Only 2 of 65 children who started theophylline treatment with slow-release preparations in the dosage we recommended (McKenzie and Baillie, 1978) had side effects that might have been attributable to theophylline, but in neither was the blood level >20 μg/ml.

We found that the incidence of nausea and vomiting in children treated with choline theophyllinate or plain theophylline (the preparation used in the Hammersmith/Denver study (Hambleton *et al.*, 1977)) was high (McKenzie *et al.*, 1978) and that compliance, as others have found (Eney and Goldstein, 1976), was poor. These side effects may occur even when levels are within the therapeutic range or below it. We now rarely use these compounds, preferring the slow-release preparations.

We agree that serum levels may be more constant in those children with fast clearance rates if the slow-release preparation is given every 8 hours. However, it must be remembered that the efficacy of theophylline is proportional to the logarithm of the blood level (Mitenko and Ogilvie, 1973). Trough levels <10 μg/ml may give satisfactory control for many children and an extra dose just to raise the blood level would therefore be unnecessary.

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Incidence of dental caries in coeliac children

Sir,

Referring to the letter on this subject (*Archives*, 1979, **54**, 166), we have submitted a paper entitled 'Gastroenteritis, coeliac disease, and enamel hypoplasia' to the *British Dental Journal*. One of the problems in such a study was the difficulty in obtaining, for histological section, teeth with enamel hypoplasia. The hypoplastic lesions are often destroyed by dental caries. We were lucky to obtain specimen teeth, in spite of the fact that we have been observing coeliac children for 20 years.

The lesions that were on the permanent incisors and on the first permanent molars were produced at the end of the first year of life. It is possible to detect the lesions before the teeth erupt by means of *x*-rays. This allows appropriate preventive or therapeutic measures to be instituted as soon as the tooth erupts.

J. MILLER AND M. D. H. SMITH
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Mr Fulstow comments:

I should like to thank Mr Miller and Mr Smith for their comments and I look forward to reading their paper in the *British Dental Journal.*

E. D. FULSTOW
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Fucidic acid in Gunn rats. No influence on serum bilirubin concentration

Sir,

When drugs which compete with bilirubin for albumin-binding sites are injected into homozygous Gunn rats there is a decline in the level of serum bilirubin. After long-acting sulphonamides, for instance, serum bilirubin decreases to between 10 and 20% of the baseline concentration (Ballowitz and Hanefeld, 1976). The displaced, now unbound (free), bilirubin moves out of the plasma mainly into adipose tissues, including the brain, where it may lead to kernicterus. This was first described for sulphisoxazole (Gastrisin) by Johnson *et al.* (1959).

During the last decade several other drugs that are commonly used in nurseries have been subjected to appropriate tests (Brodersen, 1974; Yeary and Davis, 1974; Rayner *et al.*, 1978). Fucidic acid was not among them, as this substance is not often prescribed during the first days of life. However, we recently had to infuse this antibiotic into a newborn baby suffering from severe staphycococcal sepsis and osteomyelitis, the staphylococci being resistant to most other antibiotics.

We therefore tested IV 'fucidin soluble' ampoules (Thomae GmbH Biberach a.d. Riss, Germany) in 3- to 5-day-old homozygous, jaundiced Gunn rats. We also gave them an oral suspension 'z 141–EXT.7'+ (not yet available in Germany) containing 5 g fucidic 2·2 imidoethanol per 100 ml. The IV dose was 10–50 mg/kg, the oral dose—given by gavage—50 to 2000 mg/kg. LD_{50} of the 2 preparations, which we investigated in 3- to 5-day-old, heterozygous, nonjaundiced Gunn rats, differed markedly. It was between 50 and 100 mg/kg after IV and 1000 mg/kg after oral application. There was no effect on levels of serum bilirubin. Half an hour after IV and 3 hours after oral administration, the highest doses decreased the levels of serum bilirubin to about 80% of the baseline concentration (7·1–9·3 mg/100 ml; 121–159 μmol/l), a similar decline to that which occurs after a saline injection.

We conclude that neither fucidic acid nor the stabilisers in the intravenous preparation is a strong competitor for albumin-binding sites.

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Spina bifida and maternal Rh blood type

Sir,

Spina bifida cystica (myelomeningocele) is a relatively common birth defect (one in 500 to one in 200 live births) whose aetiology is not known, although it has been suggested that a patient's children and siblings have an increased risk (Bergsma, 1973). Unfortunately, preventive measures, other than genetic counselling to affected families and prenatal screening for high α-fetoprotein levels in patients at risk, are nonexistent. We should like to report the results of a pilot retrospective study on children with spina bifida, whose parents are members of the Houston chapter of the Spina Bifida Association of America. We examined 28 cases and found that more mothers had Rh- blood type in this population compared with the general population ($\chi^2 = 6\cdot45$, confidence interval 0·02%). We found about twice as many mothers with Rh- blood type in our sample (i.e. incidence 15%) (Wiener, 1954). We are currently planning to study a much larger sample and we hope to determine the Rh-blood type of parents and all siblings, and compare the incidence of Rh-blood incompatibility, Rh haemolytic disease, early postnatal jaundice, and transfusions. We have found no reports that suggest a possible relationship between maternal Rh-blood type and spina bifida.

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Book reviews

Pediatric Kidney Disease (in two volumes). Edited by Chester M. Edelmann. (Vol. 1: pp. 573; illustrated + tables. Vol. 2: pp. 769; illustrated + tables. £35.00 each volume, hardback; cased. Little Brown: Boston. 1978.

This is the 4th multiauthor textbook of paediatric nephrology in English to appear and it is the longest and most comprehensive with more than 100 contributors. It covers the whole of nephrology including physiology and renal development, pathogenesis of renal damage, clinical investigation, complications of renal disease and their management, congenital and hereditary kidney disease, glomerulonephritis, nephrotic syndrome, systemic illness and nephritis, tubular disorders and, finally, urinary tract infection and 80 pages of paediatric urology. 85% of the authors are from the USA and most are particularly associated with the Albert Einstein College of Medicine, New York, an institution which has played an important rôle in the development of paediatric nephrology and especially developmental physiology of the kidney. The editor himself has contributed considerably to these studies. The book reflects these strengths. Some of the chapters are magnificent; that by Dr Spitzer on renal physiology and functional development has 103 pages and over 1300 references providing almost a book on its own. Other chapters dealing with basic concepts, laboratory and animal research, and pathological mechanisms are equally good. The clinical sections seem by comparison to be weaker and less well organised. For instance the management of acute renal failure is dealt with in two separate chapters, beginning on pages 466 and 1108, and with renal failure and nephritis the number of authors dealing with different aspects of the problems does not make it easy to obtain practical clinical advice. No mention is made of hypovolaemia as a major complication in minimal change nephrotic syndrome, or of the value of dynamic renal scintigraphy in acute renal failure, or of congenital duplex kidneys and ectopic ureterocele, in spite of 25 pages on urologic trauma in childhood; it is not clear whether all children with urinary tract infection should have a micturating cystogram. Other minor criticisms could be made and, overall, fewer authors and some reorganisation of and within chapters would improve the book but none the less it is a major achievement. The information is not given in other textbooks on nephrology or paediatrics and the book reflects the emergence of paediatric nephrology as a specialised area of clinical and experimental work. It is well produced, reasonably (by current standards) priced, and while essentially a reference book, it is one which will be eagerly sought by doctors caring for children with kidney disease.

CYRIL CHANTLER

Surgical Management of Juvenile Chronic Polyarthritis. Edited by G. P. Arden and B. M. Ansell. (Pp. 281; illustrated + tables. £15.60 hardback.) Academic Press: London. 1978.

This 275-page monograph covers a unique experience of 30 years' treatment of juvenile chronic polyarthritis in the rheumatic unit at Taplow. With a quoted incidence of 24 per 100 000 of the population, few surgeons or physicians outside a special unit can have wide experience of the management of this condition. This book, under its 2 editors and 8 contributors, provides that information and experience, and deals not only with surgery, but also with radiology, anaesthesia, pathology, rehabilitation, and general medical problems. It emphasises the necessity for teamwork and the value of joint clinics where discussions can take place about the treatment of diseases such as this which have such widespread effects.

Surgery and anaesthesia are not without their hazards in this crippling disease, but advances in joint replacement are revolutionising what can be offered to these patients. The chapter on anaesthetic problems and the use of ketamine in patients in whom intubation is dangerous, if not impossible, is most interesting. Replacement of the hip joint is now a common and successful operation. However, the particular problems presented by these children and the special methods used to overcome them have been learnt by hard experience which is invaluable to other surgeons. Knee joint replacement remains a problem. Several types are being assessed, but none has become established in the way that the hip joint has done. Hands and feet have not been forgotten, particularly the importance of simple conservative methods, such as splints and supports.

Rehabilitation is rightly emphasised. The devastating effect in terms of joint stiffness which can result from taking a simple biopsy of the knee in the young child, is pointed out several times. The use of a prone lying couch, regular exercises, swimming, rest, and sometimes work splints, stress the importance of continuous treatment in daily life as well as in hospital. I would certainly recommend this short, readable book for anyone interested in the formidable problems presented by these children.

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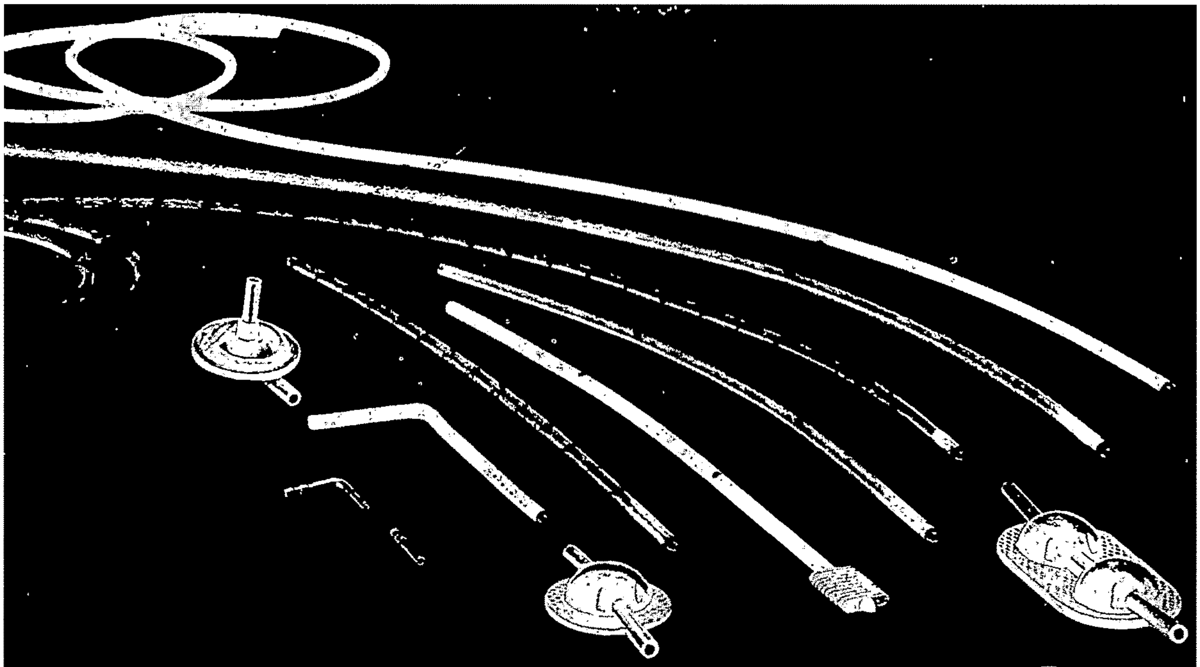

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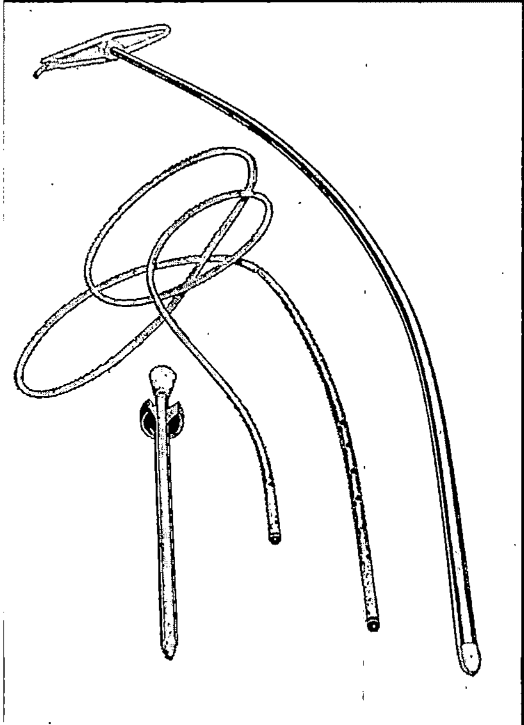

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Review article

Juvenile diabetes mellitus

Possibility of prevention

J. W. FARQUHAR

Department of Child Life and Health, University of Edinburgh

Knowledge of insulin-dependent juvenile-onset diabetes (JOD) has grown quickly during the last 5 years, particularly in three areas. (1) A small number of viruses may be associated with the development of JOD. (2) Certain genetic markers (HLA types) provide a means of identifying who is vulnerable. (3) Autoimmunity may cause more or less rapid pancreatic islet cell destruction and may be initiated in those who are vulnerable by specific virus action. The gene responsible for diabetic vulnerability may be identified in the next decade. It may then be possible to prevent JOD. Such research could be as profitable as the development of new treatment techniques.

Children form one-tenth of the recognised diabetic population in Europe and North America. The disease affects about one child in 800 under 16 years (Bloom *et al.*, 1975; Calnan and Peckham, 1977) and one young person in 300 under age 26 (Wadsworth and Jarrett, 1974). Many physicians share the impression that it is becoming more prevalent (Calnan and Peckham, 1977; Craig *et al.*, 1977).

JOD is generally insulin-dependent from the time of diagnosis or soon afterwards. The child's daily insulin injections, spaced meals, and monitoring tests may be simplified to an acceptable routine (Farquhar, 1972, 1976; Craig, 1977) but even the lightest impositions can exaggerate such behavioural flaws as already exist in him or in his family. This can cause unhappiness and tragedy (MacGregor, 1977). Mothers of diabetic children can suffer nervous strain (Olatawura, 1972) and need generous support and treatment.

For the diabetic child lies the possibility of a major disability—such as retinopathy, nephropathy, and neuropathy. Thus in the UK almost 1000 diabetics are added annually to the register of blind persons; diabetes is, at the least, the third most common cause of blindness in the age group 30–49 years (Sorsby, 1966). From the Joslin Clinic, White (1960) reported some degree of retinopathy in 93% of diabetics after 20 to 40 years. While optimal control may limit the risk (Farquhar, 1977), these statistics carry the disturbing implication that many diabetic children will have some visual handicap by the time they are between 30 and 50 years, and likely to have dependent families. The other results of microangiopathy and ischaemic heart disease are just as crippling and more life-threatening, life expectancy being about two-thirds that for normal children (Bloom *et al.*, 1975).

To the possible unhappiness and anxiety of patients and relatives must be added the cumulative economic burden to the community—hospital admissions for restabilisation, medical supplies for home control, related educational and social needs, extra care in pregnancy, and (when diabetic disability arises) long-term support for the individual and his dependants. Such massive annual cost makes attractive the direction of financial resources towards research into cure or, better still, prevention. 'Cure' may be possible when effective human pancreatic islet transplantation (*Lancet*, 1975; Turtle, 1977) or the implantation of an 'artificial pancreas' or of crossed-species islets in a micropore chamber (Gates and Lazarus, 1977) can be offered to all. The warning of Gajdusek (1979) about the possible transmission of slow virus in transplant tissue may be less relevant when fetal islets are used. Advances in prevention will cost much money but is there any hope? The evidence is now reviewed.

Clinical characteristics

JOD is characterised by three phases.

Phase 1. The acute and largely permanent process in

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which hyperglycaemia, ketoacidosis, and coma develop and kill in the absence of insulin treatment. Overt infection coexists or closely precedes this phase in at least one patient in 3. Less noticeable infection may be common.

Phase 2. A phase of partial recovery commonly known as the 'honeymoon' lasting a few weeks or months when only small doses of insulin are needed or, more rarely, when it may be replaced by reducing the carbohydrate intake and adding an oral hypoglycaemic agent.

Phase 3. A subacute or chronic phase of progressive intrinsic insulin inadequacy within which diabetic control has a variable cycle of ups and downs (variable energy intake and output, variable dose of insulin, and variation in the diabetic process).

The pathological process should satisfactorily explain these phases.

Epidemiology

Physicians closely concerned with diabetes have for decades noted a tendency for new patients with JOD to cluster in time and space. They experience quiet and busy years in registering new patients, obvious variation within a year, little outbreaks within small communities, and unusual prevalence in cohort analysis of older patients. Adams (1926) recorded seasonal variations, while Gunderson (1927) was so impressed by this that he asked the question 'Is diabetes of infectious origin?'

The register of newly diabetic children (age group 0–15 years) sponsored by the British Diabetic Association gave much epidemiological information (Bloom *et al.*, 1975; Gamble and Taylor, 1976). It recorded a seasonal variation in incidence in children aged 5–15 years with peaks in the autumn and winter, although little relationship to environmental temperature was noted (Gamble, 1974). A seasonal incidence in children was also recorded by Rolles *et al.* (1975), but denied by Barbosa *et al.* (1976). Preschool children, on the other hand, showed less variation and no seasonal pattern. Age incidence in the register seems to be bimodal with peaks at about 5 and 11 years when children are joining primary and secondary schools. There is no consistent relationship to growth or puberty. During the years 1973–74 the incidence varied from 4·78 to 10·61 per 100 000 children each year geographically. In spite of a financial incentive to notify new cases to the national register, it seems that staff in some parts of the country (for example London) were less likely to do so than in other parts. Thus the register probably underestimated the number of children with JOD.

Lastly there were some surprising outbreaks within families—diabetes developing almost simultaneously in 5 cases in two years. In one family there were 3 siblings. Does JOD result from infection? If so how often, and is it preventable?

An environmental factor

The possibility of an infective cause was raised by Harris (1899) when he described the rapid development of diabetes after mumps. The same association was described by others—such as Cole (1934), Melin and Ursing (1958), Hinden (1962), and McCrae (1963). Since then there have been many reports on animals and man. Indeed Brown (1956) stated 'the most common cause of diabetes in children is a systemic infection which injures the islets of Langerhans'.

Animal diabetes. The virus of foot-and-mouth disease was linked with the development of diabetes mellitus in some cattle by Barboni and Manocchio (1962). In 1965 Craighead reported an association between encephalomyocarditis (EMC) virus and pancreatitis in mice. Subsequently he showed that EMC virus multiples in the pancreatic β-cells of mice to produce diabetes mellitus and pancreatic islet histology which closely resembled that in JOD (Craighead, 1975, 1976, 1978). He showed that the islet insulin increased 3-fold before falling to very low values. These and further studies by Ross *et al.* (1975) and Boucher *et al.* (1975) established that diabetes mellitus was produced only when a particular breed of mouse was used and only when the infection was caused by the M variant of EMC virus. Five very similar strains failed to invade the pancreatic β-cells. This work was reviewed by Notkins (1977) and indicated the need for a genetic factor both in the host and in the infecting agent. Another interesting observation was the failure, even of M strain EMC virus, to induce diabetes in athymic (nude) mice although it did so in suitable controls (Buschard *et al.*, 1976).

Similarly, Coleman *et al.* (1973, 1974), Gamble (1975), and Smith and Deibel (1975) showed that a specified breed of mouse could be made diabetic by infecting it with Coxsackie virus B4, the pancreatic islet histology again resembling the findings in JOD. This is particularly interesting in view of observations in man.

Child diabetes. The association with mumps seems clear but it may contribute very little to the annual incidence of JOD. Notkins (1977) stated the obvious—that mumps is common but complicating diabetes is rare. It should be remembered however that months (Melin and Ursing, 1958), or years

(Sultz *et al.*, 1975), may separate the infection from the recognition of diabetes. The report of a patient with JOD after inoculation with a live-attenuated mumps vaccine (Sinaniotis *et al.*, 1975) will be discussed later.

Rubella virus

The development of diabetes was described in a patient after congenital rubella (Menser *et al.*, 1967) and was followed by a series of well substantiated reports on other patients (Menser *et al.*, 1978), many of whom had insulin-dependent JOD. Experimental work with rubella virus on pregnant rabbits produced histological changes in the fetal pancreatic β-cells similar to those produced in mice by EMC virus.

Coxsackie B virus

British research focused attention on the possible role of Coxsackie B virus. This began (Gamble *et al.*, 1973) with the observation that Coxsackie B4 (CB4) virus was more often found in new patients with JOD aged 10 to 19 years than in control subjects, although the significance of this may now be uncertain. A matching seasonal incidence was also noted. This hypothesis is being developed and applied to HLA typing (Cudworth *et al.*, 1977).

Acute JOD has been described in a boy of 18 months who had a high titre of CB2 and of CB-specific IgM (Wilson *et al.*, 1977). Three unrelated young adults developed acute diabetes in association with symptoms suggesting a virus illness (Gibbs, 1974). All 3 had ECG changes suggesting a myocarditis which was assumed viral.

Nine of a cluster (in time and space) of 12 patients with JOD were investigated by Huff *et al.* (1974); 8 of the 9 had suffered a recent 'viral illness', mainly respiratory. No single virus test in a panel of 26 common viral agents was positive in all, but CB3 was proved in 33%, compared with 6% of the controls.

In one family reported by Nelson *et al.* (1977) in which both parents were diabetic, 3 of their 5 children developed classical JOD within 4 months. One had an attack of Bornholm disease one month before developing diabetes and was found to have high antibody titres to CB1 and CB5. Another had a low antibody titre to CB2.

Baum *et al.* (1974) tested 11 new patients with JOD for evidence of recent infection by a wider range of viruses including CB1–5, but none was found.

A population was studied in the Pribilof Islands (Behring Sea) 5 years after an epidemic of CB4 infection. Those with serological evidence of previous infection were given glucose tolerance tests, but there was no evidence of increased prevalence (Dippe *et al.*, 1975). Subsequent appreciation of the susceptibility to diabetes of persons sharing the same HLA type (described later), and the possible protection of others, robbed the Pribilof study of some of its value. The indigenous Alaskan in these islands is not Caucasian and might not have been vulnerable to CB4 infection (Cudworth *et al.*, 1975). This point was agreed by Dippe *et al.* (1975).

So the case remains unproved but may be partly true. Kono (1976) stated that CB3 and CB4 can be isolated from the human infant's pancreas. Further work on this association is justified in the light of the reports on fetal rubella (Menser *et al.*, 1978).

Other infections

A major epidemic of infective hepatitis in West Africa was reported to have caused diabetes mellitus (Adi, 1974; Osuntokun, 1974) and, in Australia, a young man became acutely diabetic during an attack of infectious mononucleosis (Burgess *et al.*, 1974).

An inherited factor

Diabetes in relatives. The experiments already described with viruses and mice established that, for the mouse model, the genetic complement of the host is essential to the production of diabetes mellitus. This will now be examined by looking closely at diabetes mellitus occurring in relatives.

Children of diabetic mothers

Long-term follow-up studies on large populations of such children are difficult but information (Farquhar, 1969) strongly suggests that the incidence of diabetes should be high. White (1959) reported that 9% of such offspring were diabetic by age 14 and that a further 14% had chemical diabetes (see below). It is important to remember that most of the mothers in the Edinburgh study (Farquhar, 1969) had type 1 diabetes—that is, they were insulin-dependent young diabetics.

Children of conjugal diabetics

One study of such children (Cooke *et al.*, 1966) gave an incidence of 4·4%, and there were earlier studies by West (1960), Post (1962), and Simpson (1964). In the light of later knowledge it is interesting to find that diabetes was found more often among children whose parents had become diabetic early in life. The facts that earlier workers did not discriminate between JOD and MOD (maturity-onset diabetes), and that chemical testing for diabetes was too often more a matter of opinion than of science, lead to difficulties of interpretation. Thus the study by Rojas *et al.* (1969) noted the ages of the young people but not of the parents at the time of their becoming diabetic. The parents cannot therefore be assigned to the JOD or MOD group. It was concluded that the only revealing test was a poor initial insulin response to glucose in those whom it had been decided were 'prediabetic', postulated as a defective glucose-responsive mechanism for insulin secretion. In another paper Kahn *et al.* (1969) estimated from such tests that 40% of those born to conjugal diabetics had evidence of chemical diabetes.

Radder and Terpstra (1975) studied the children of patients with conjugal MOD, mean age at diagnosis 61 years. About 45% of these children were chemically diabetic on oral glucose tolerance tests but fewer than one child in 4 had previously been diagnosed. The diagnosis related to the offspring being overweight. Similarly in the study by Tattersall and Fajans (1975a) most of the parents had MOD, with a mean age at diagnosis of 54·5 years. The 'children' had a mean age of 32·6 years and 28% had impaired glucose tolerance, 2% had JOD. It was estimated that 60% would give positive results to tests by age 60 years and it was rightly concluded that results based on the offspring of 2 patients with MOD cannot be assumed to be relevant to children of 2 patients with JOD.

Siblings of diabetics

Investigators in the 1950s and 1960s half-expected to find 'heterozygotes' with abnormal glucose tolerance (chemical diabetes) among the siblings of patients with JOD. Indeed, Fajans and Conn (1954) found 19% of young adults with diabetic glucose tolerance tests. When such siblings develop insulin-dependent diabetes the diagnosis is not in doubt, but when they do not, their subjection to batteries of tests and the correlation of results widen the range of possible interpretation (Kahn *et al.*, 1969).

Thus 16% of siblings were classified as being chemically diabetic by Jackson *et al.* (1968) and 11% were so classified by Rosenbloom *et al.* (1972). Rosenbloom (1975) subsequently investigated glucose tolerance in a large group serially and found that 0·5% had overt JOD and that fewer than 5% had chemical diabetes by his standards. Adult siblings were studied by Kobberling *et al.* (1969) who estimated that 39% had chemical diabetes. It now seems less likely that their diabetes was that of the propositi.

Identical twins

A selected series of identical twins was studied and reported (Pyke and Taylor, 1967; Pyke *et al.*, 1970; Nelson *et al.*, 1975). More than half the pairs have proved to be discordant for diabetes but Rosenthal *et al.* (1976) argued that there would be concordance in at least 80% if the series were followed up. Certainly concordance for MOD is almost 100% in identical twins after age 40 (Gottlieb and Root, 1968; Tattersall and Pyke, 1972). The latter study is nevertheless interesting in that the older the discordant twins become the more likely they are to develop insulin-dependent JOD. The results of extensive virus studies are given by Nelson *et al.* (1975). While it is disappointing that there was little difference in antibody levels between the diabetic and unaffected twins, it was acknowledged that only a few were examined within 2 years of diagnosing diabetes. It was suggested that the non-diabetic twins may have had too low a dose to cause pancreatic damage.

Triplets, claimed to be monozygotic, discordant for diabetes were described by Ganda *et al.* (1977). The first developed JOD at age 13 years. The second had normal glucose tolerance tests until she became diabetic at age 21. The third remains normal on testing.

Parents and ancestors

The clearer separation of diabetes mellitus into two main groups—type 1 or JOD, and type 2 or MOD—has made family studies more meaningful. Thus MacDonald (1974) compared the ancestors of patients with type 1 with a control group and found an equal incidence of diabetes mellitus, surprising as this may be for several reasons. Separate groups of JOD and MOD (of the young) were studied by Tattersall and Fajans (1975b). Only 11% of those with JOD had a diabetic parent compared with 85% of those with MOD. In only 6% of those with JOD had the disease been present in three generations compared with 46% of those with MOD. These studies give further evidence of genetic heterogeneity in diabetes mellitus.

Disease associations

Insulin-dependent JOD can be associated with disorders ranging remarkably from Down's syndrome (and other chromosomal abnormalities) to coeliac disease, and from autoimmune endocrinopathies to nerve deafness and optic atrophy. The nature of the diabetes may differ in the disorders listed in the Table but there is doubtless a message in these associations for him who finds the cypher.

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lucose-6-phosphate dehydrogenase deficiency
ype I glycogen storage disease
aemochromatosis
untington's chorea
yperlipaemia, diabetes, hypogonadism, and short stature syndrome
yperlipoproteinaemia III
yperlipoproteinaemia IV
yperlipoproteinaemia V
olated growth hormone deficiency
aurence-Moon-Biedl syndrome
eucoderma
ipoatrophic diabetes
luscular dystrophy
lyotonic dystrophy
cular hypertension induced by dexamethasone
ptic atrophy and diabetes
lereditary relapsing pancreatitis
hotomyoclonus, diabetes, deafness, nephropathy, and cerebral dysfunction
ineal hyperplasia and diabetes
cute intermittent porphyria
haeochromocytoma
rader-Willi syndrome
etinitis pigmentosa, neuropathy, ataxia, and diabetes
chmidt's syndrome
Verner's syndrome

family possessing diabetic relatives, picks out this r that child's pancreatic β-cells for destruction. As n the selectively bred mice, an unknown number perhaps all) of these individuals are genetically ulnerable. Those at greater than normal risk can ow be identified by HLA tissue-typing because hey possess in greater than normal degree a number f identifiable antigens. Minor differences, caused erhaps by inherent instability, in relevant alleles nay even explain the surprising discordancy for liabetes between monozygous 'identical' twins.

The antigens associated with JOD are B_8, BW_{15}, $_{18}$, BW_{35}, A_1, AW_{30}, DW_3, DW_4, CW_3, DRW_3, nd DRW_4. Reports on individual antigens are riefly reviewed. Changes in nomenclature are ommon and can be confusing.

ndividual associations. Cudworth and Woodrow 1974) and Nerup *et al.* (1974) noted that B_8 was nore common in patients with JOD—54% compared with 31·8% in controls. Others found it to be ven more common. The relative risk for developing JOD was given as 2·12 but was later increased in hose under 30 years to 2·5 (Cudworth and Woodrow, 1976; Nerup *et al.*, 1976). It was found to be increased also in congenital rubella (Menser t al., 1974). The significantly higher representation of B_8 in differing degree in JOD has been reported in many papers from different communities (Löw *et al.*, 1975; Rolles *et al.*, 1975; Barbosa *et al.*, 1976; Landgraf *et al.*, 1976; Morris *et al.*, 1976; Pointel *et al.*, 1976; Savi *et al.*, 1976; Vialettes *et al.*, 1976; Barta and Simon, 1977; Illeni *et al.*, 1977; Koivisto *et al.*, 1977; Ludwig *et al.*, 1977). Illeni *et al.* (1977) found the increase in B_8 to be significant in the 0–5-year age group. This antigen was found not to be increased beyond the expected normal in Sardinia despite a high prevalence of diabetes (Contu *et al.*, 1976). It should be noted that HLA-B_8 is uncommon in the Aleutian people of the Pribilof Islands (Menser *et al.*, 1974).

Cudworth and Woodrow (1974, 1975a,b, 1976) reported increased representation of BW_{15} and a relative risk of 1·85. Similar experience was recorded by Nerup *et al.* (1974, 1976), Löw *et al.* (1975), Morris *et al.* (1976), and Solow *et al.* (1977), but not in rubella by Menser *et al.* (1974, 1978). In Sardinia, Contu *et al.* (1976) found it in 11·4% of patients with JOD but in only 2% of the rest. It was not increased however in studies made in France (Pointel *et al.*, 1976) or Finland (Koivisto *et al.*, 1977).

The coexistent increased representation of B_8 and BW_{15} may have a significant effect. Nerup *et al.* (1976) suggested an increased risk to siblings of the propositus, while Koivisto *et al.* (1977) found it at its greatest when JOD coexisted with coeliac disease. Barta and Simon (1977) found increased representation of B_8, but not of BW_{15}, in Hungary. When they looked at coexisting B_8 and BW_{15}, however, it was present in 15–16% of patients with JOD but in only 0·9% of controls. From this they calculated relative risks for B_8, and for B_8 and BW_{15} at 2·027 and 18·25 respectively. Cudworth *et al.* (1977) however estimated the relative risk of B_8 and BW_{15} at 5·59.

Cudworth and Woodrow (1976) reported increased representation of B_{18} in patients with JOD and calculated the relative risk to be 2·56. According to Vialettes *et al.* (1976) B_{18} occurs in 26·6% of those with JOD compared with 11·8% in the general population.

Contu *et al.* (1976) reported that BW_{35} was present in 29·2% of patients with JOD compared with 12·5% of the nondiabetic population. In Italy Savi *et al.* (1976) found it was present in 38% of those with JOD compared with 23% in controls in Parma, while Illeni *et al.* (1977) reported from Milan that BW_{35} was significantly decreased in those with JOD.

Morris *et al.* (1976) found A_1 to be over-represented in insulin-dependent diabetics, the proportion being greater in those with thyrogastric antibodies and persistence of pancreatic islet cell antibodies for more than 5 years (see later). Vialettes *et al.* (1976) found the antigen was almost twice as common in diabetics described as 'low-insulin responders' to glucose, likelier perhaps to be MOD or MODID (maturity-onset diabetes insulin-dependent).

AW_{30} antigen is increased (Illeni *et al.*, 1977) in JOD patients diagnosed between October and January and this could be related to a specific seasonal infection.

DW_3 and DW_4 are associated even more strongly than B_8 and BW_{15} with JOD (Nerup *et al.* 1976). DW_3 and DW_4 were found in 80% compared with 24% in controls, as stated also by Hsu *et al.* (1977); its importance was also noted by Bottazzo and Doniach (1976) and Irvine *et al.* (1977a).

The increased representation of CW_3 in JOD is described by Ludwig *et al.* (1977).

DRW_3 and DRW_4, the alloantigens found on B-lymphocytes, are believed to carry a relative risk of 4·5 and 2·5 respectively (Schernthaner *et al.*, 1977).

The importance of B_7 (Ludwig *et al.*, 1977) lies in its significantly *low* representation in JOD (13·2% v. 26·8% in the normal population).

The technique of HLA-typing now makes possible the recognition of an individual who is likely to develop JOD when appropriately challenged. The exact locus and nature of the fault is likely to be found as HLA mapping continues.

Viral association. Of HLA-B_8-positive patients with JOD reported by Rolles *et al.* (1975) 81% presented between October and the end of February, whereas those with HLA-B_8-negative JOD presented throughout the year. The late autumn and winter period coincides with the highest incidence of Coxsackie B virus infections. This was not the experience of Barbosa (1977). Cudworth *et al.* (1977) recorded twice as many new patients with JOD in autumn/winter as in spring/summer. They reported BW_{15} clustering in winter but not in the previous autumn. They also reported that new patients with JOD with BW_{15}, and especially with B_8 and BW_{15}, had higher neutralising antibody titres to Coxsackie B virus strains 1–4.

β-Cell destruction and autoimmunity

Histology. Death is rare in diabetic children and adolescents who attend good clinics. Pathologists therefore have little chance to examine the pancreas from recently diagnosed young diabetics. Gepts (1965, 1976) has attracted material from other centres and has acquired great experience. He described a characteristic lymphocytic insulitis in the pancreas of young people dying within 6 months of diagnosis. This looked like a response to direct viral aggression or an immune reaction and it is seldom seen in patients who die after being diabetic for one year. It may well indicate the process by which β-cell function is more or less suddenly interrupted, recovers briefly, and is then lost steadily. Similar histology was described in a child who died from congenital rubella (Bunnell and Monif, 1972), and the virus may persist in human pancreas for months or years (Cooper *et al.*, 1965). Gepts *et al.* (1977), using new immunocytochemical methods, found that β-cells could be identified in JOD of recent onset. In chronic JOD the atrophic islets are composed mainly of glucagon, and of somatostatin cells. In addition the JOD pancreas contains ribbon-like cells considered to secrete pancreatic polypeptide. Hyperplasia of such 'HPP cells' in JOD is thought to represent atypical islet regeneration induced by severe and prolonged injury to pancreatic endocrine tissue.

β-Cell changes, similar to those found in mice made diabetic by EMC virus, were consistently found in the offspring of rabbits infected with rubella during pregnancy (Menser *et al.*, 1978).

Association with autoimmune diseases. A clinical association between diabetes mellitus and diseases characterised by organ-specific autoimmunity is well recognised and documented (Carpenter *et al.*, 1964; Irvine *et al.*, 1967) and its familial character has been reported by Bottazzo *et al.* (1978). Antibody evidence of thyroid and gastric autoimmunity was given by Irvine *et al.* (1970) who concluded that there seemed to be 'a disorder of the immunological system related to insulin-dependent diabetes'. The subject was reviewed by MacCuish and Irvine (1975).

Pancreatic islet-cell antibodies (PICA). These were reported by Bottazzo *et al.* (1974) and have attracted much attention and caused some controversy, but their existence is not in doubt. Debate continues on whether they result from pancreatic islet cell damage or represent the attacking process. They are certainly associated more with insulin-dependent JOD than with MOD, although the latter may be divisible into those with and those without PICA. Those patients with MOD and PICA may be controlled by oral hypoglycaemic agents, and Irvine *et al.* (1977a, b) suggested that they represented a less severe form of JOD in those who will eventually require insulin. PICA are classified as IgG (MacCuish *et al.*, 1974a; Lendrum *et al.*, 1975). According to Lendrum *et al.* (1976) they are found in fewer than 2% of non-diabetics, in 5% of insulin-independent diabetics, and in 38% of those who are insulin-dependent. They are detectable however in 85% of JOD immediately after diagnosis and decrease with time. Irvine (1977) suggested that in some there is such sudden islet cell death that PICA are not found at any stage. If they represent only the response to attack, then their usefulness in prevention or restriction of damage is limited; but Irvine *et al.* (1976) gave some evidence of their presence in nondiabetic patients with other autoimmune problems.

Tests of immune response. Cellular sensitivity to an extract of human pancreas assessed by MacCuish *et al.* (1974b), using the leucocyte migration test, gave abnormal results only in young JOD. Patients with JOD and controls were tested by Richens *et al.* (1976) for cellular sensitivity to pancreatic preparation, liver mitochondrial, and CB4 virus. The JOD response was again increased to pancreas and to mitochondriae but it did not differ from controls when tested with CB4. There was a suggestion of CB4 hypersensitivity 3 months after diagnosis.

Huang and Maclaren (1976) demonstrated significant cytoadherence and cytotoxicity to human insulinoma cells *in vitro* when compared with controls. They favoured the hypothesis that JOD is a 'disease of autoaggression' and that lymphocytes and not antibodies deliver the attack on pancreatic β-cells. The role of T-cell suppressor function was studied by Horowitz *et al.* (1977). It was successfully demonstrated in all controls but was deficient in 6 of 9 patients with JOD.

The destructive device. What changes an apparently healthy child into one with JOD within days or weeks? Rubella and mumps certainly seem to trigger a genetic time-bomb with a delayed action system. While it is impossible to disregard the negative virus study from Oxford (Baum *et al.*, 1974), it only excluded appropriate antibody responses to that panel of viruses about which evidence was sought. Recent history confirms that previously unrecognised micro-organisms are responsible for serious diseases of which the aetiology was unknown (Gajdusek, 1979). Reports strongly suggest the involvement of Coxsackie B viruses and there may be others. Alternatively a failure to raise antibody may be a meaningful observation, but this would then be out of step with the fact that CB4 antibody was more common in patients with JOD than in controls (Gamble *et al.*, 1973). Perhaps a time factor, as in rubella, or fatigue or stress, as in paralytic poliomyelitis, also operate. Certainly a small but varied group of infective triggers to the device would explain the epidemiological facts.

Only a small minority of the population carries the next stage of the destructive device. Alternatively it is made safe by age. Thus either all potential patients with JOD are triggered in their early years or some escape the initial attack (virus) when the device is sensitive. Age certainly has some influence as it would seem, for example, that rubella is only insulopathic when prenatally acquired although this has still to be proved. Few people escape rubella and mumps in their first 20 years and scarcely any become quickly diabetic in association with it.

The usefulness of HLA-typing in the identification of those who are vulnerable is apparent, but why do these particular types carry an increased risk of β-cell destruction? Intra-HLA recombination has been shown by Suciu-Foca and Rubinstein (1976) to be less than 1% in offspring of apparently normal parents (6 crossovers in 2000 babies in 600 families). They claim it to be 15% however in families containing one or more person with JOD. They suggest the existence of a gene which increases the rate of recombination (that is chromosomal instability) in at least a segment of human chromosome 6. In cases where the individual is homozygous it may be associated with the appearance of JOD. Others share this view that the specific antigens already reviewed closely adjoin an immunoreactive gene concerned somehow with the autoaggressive reaction. The β-cell receptor may favour the attachment of specific viruses. A series of possible effects follow, analagous perhaps to those in response to hepatitis B virus* (HBV) shown in the Figure, taken from Eddleston and Williams (1974). A direct attack may cause β-cell death. Alternatively the process of virus replication in β-cells is sublethal to them and the damage is mediated by a host immune response. Virus-associated antigen on the cell surface provokes a T-cell response with destruction of infected β-cells, release of virus, antibody response, and either the end of the attack (if all virus is eliminated), or reinfection of surviving β-cells. T-cell 'helper-effect' may stimulate β-cells to produce antibody which attaches to virus antigen or virus-associated antigen on the cell surface.

K-cells would then kill the antibody-coated β-cells. This reaction should be time-limited by suppressor T-cells and failure would lead to a sustained attack. Lastly there is the possibility of a delayed immune response in which T-cells, alerted to seek and kill minor deviations from normality, sustain an autoaggressive action on surviving β-cells

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*Anti-Hbs and hepatitis were in fact found more commonly in diabetics than in nondiabetics by Hasslacher *et al.* (1973) but, while more frequently seen in patients with JODs rather than those with MOD in a later study (Hasslacher *et al.*, 1977), the prevalence had fallen to that in the nondiabetics. Previous patient-to-patient transmission and subsequent improvement in disposable syringes, needles, etc. are thought to explain the change.

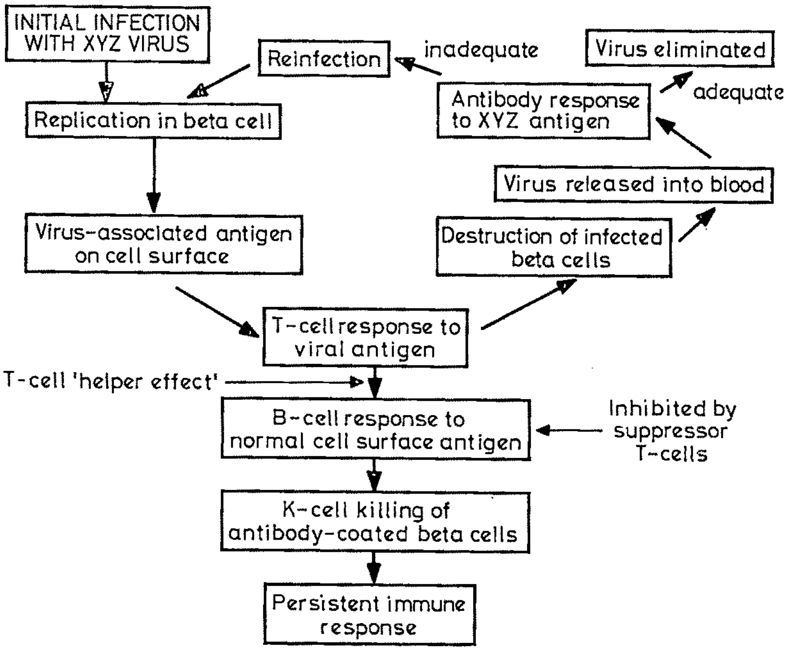
INITIAL INFECTION WITH XYZ VIRUS
Reinfection
inadequate
Virus eliminated
adequate
Antibody response to XYZ antigen
Replication in beta cell
Virus released into blood
Virus-associated antigen on cell surface
Destruction of infected beta cells
T-cell response to viral antigen
T-cell 'helper effect'
B-cell response to normal cell surface antigen
Inhibited by suppressor T-cells
K-cell killing of antibody-coated beta cells
Persistent immune response

Figure *Hypothesis for pancreatic β-cell damage and JOD.*

so that the child's own virus-modified cells maintain the process. Such a hypothesis could explain the clinical variations in JOD. Overwhelming infection could produce those cases in which symptoms of diabetes are virtually simultaneous with those of acute infection. Indeed, certain virus infections may be associated with pancreatic β-cells more often than is realised. The rare case of apparent complete recovery may represent the rare defensive success; or perhaps it is common and diabetes fails to develop.

Case report

In 1972 I admitted a 4·7-year-old girl who had suffered for a day or two from diarrhoea and vomiting. She was found to have diabetic ketoacidosis. Within hours of her admission her 20-month-old sister was admitted with identical symptoms but without diabetes. The elder child responded well to insulin and intravenous fluid. She was discharged within a week and has remained completely well for over 5 years. Her oral glucose tolerance test in 1978 and July 1979, when the blood glucose 2 hours after a glucose load was 5·2 mmol/l (93·7 mg/100 ml), was absolutely normal. The younger sister was also discharged within a week and remains well. From neither case was a virus recovered on culture. In July 1979 her blood glucose 2 hours after a glucose load was 4·6 mmol/l (82·9 mg/100 ml). The initial blood specimen from the elder child was unfortunately inadequate for a Coxsackie B neutralising antibody test. The second specimen however had a titre of 1024 for CB2. The younger (nondiabetic) child had a CB2 titre of 64 in the first and second specimens. In both sisters the titres for B_1, $_3$, $_4$, $_5$, and $_6$ were less than 16 .There was local scepticism about the significance of these results in 1972 and no further samples were taken. The stability of the younger sister's titre in 1972 may suggest a previous infection, rather than a response to the infection which led to the admission. The elder sister's titre exceeded the younger's by a factor of 16. Does this imply that the infection was more severe or that the response was exaggerated? And why, if the infection was an old one, did the diabetes develop severely at the time it did and as a brief phenomenon?

Between these two extremes may lie a range of diabetic progress reflecting the autoimmune response, the acute episode, the 'honeymoon', β-cell atrophy, the development of ribbon-like cells, secretion of polypeptide, and the downward drift of insulin secretion, with oscillations, especially during re-encounters with the virus, until a steady diabetic state is achieved. The contention (Irvine *et al.*, 1977a) that some young diabetics controlled on oral hypoglycaemic agents for varying periods until insulin injections are obligatory are JOD in the making (MODY) rather than MOD is consistent with this. PICA in blood would then be expected for a much longer period.

The observation by Block *et al.* (1973) that C-peptide may be detected for several years after diagnosing JOD signifies continuing but failing insulin secretion. It has been repeated recently by Werther *et al.* (1978).

Speculation

It is now possible to screen by HLA-typing the offspring and the siblings of patients with JOD for vulnerability. It is costly as an individual test but, if there were a means of protection, such an initial outlay would be miniscule compared with the cost and the suffering involved in a life-time of diabetic care. Rubella vaccine should eliminate the presumably small problem of future JOD being produced by prenatal rubella infection. Mumps vaccine is available but more information is needed about JOD arising after vaccination. Such protection however is unlikely to contribute much to a programme designed to eliminate JOD.

A polyvalent CB virus vaccine is presumably possible and could prevent much morbidity other than diabetes. As with mumps vaccines, clinical trials on people likely to be vulnerable would need to be conducted with care. Once pronounced safe, it might be better to immunise all offspring and all siblings of patients with JOD, rather than to categorise them by HLA-type for vulnerability. In either, the obstetric history of birthweight for gestational age and for fetal malformations would be of great interest. A study of vaccinated and unvaccinated siblings might help to establish the aetiological role of CB virus strains.

Whether the use of highly-purified porcine insulins for maternal control or fastidious blood glucose control during diabetic pregnancy will prevent pancreatic islet fibrosis in the fetus and future JOD is still a matter for speculation, and a source of fetal lymphocytes for HLA-testing in early pregnancy remains unavailable. It is desirable however that such pathological material be pooled and expertly examined, as provided by the diabetic pregnancy study group in Europe. Perhaps the attachment of iatrogenic maternal insulin antibody or the overstimulation of fetal β-cells causes structural change capable of initiating an autoaggressive response. The answer may come when the gene defect, to which investigators now seem so close, is identified. The absent or abnormal response may prove correctable or the vulnerable child may be protected from its attack. Cahill (1976) optimistically says, 'New cases of juvenile diabetes may be prevented if our present rate of knowledge about the disease continues to grow over the next 2 or 3 years at the rate that it has for the past 5 years'.

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Status asthmaticus in children

A one-year study

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SUMMARY 50 children were admitted on 72 occasions during one year in status asthmaticus, defined as wheezing not relieved by two doses of bronchodilator 4 hours apart. At least one-third of children were hypercapnoeic on admission. They were managed with either oral prednisolone and nebulised salbutamol or IV aminophylline and hydrocortisone in addition to salbutamol. Those with peak expiratory flow rates of >25% expected for height were satisfactorily managed on the oral regimen. One child needed assisted ventilation. 73% were fit for discharge within 4 days and more than half of them needed a change in maintenance treatment.

About 40 children between ages one and 14 years die each year in England and Wales from acute asthma. This represents about 10% of all deaths due to diseases of the respiratory system in the same age group and is equal to about 8% of all deaths due to motor accidents (Office of Population Censuses and Surveys, 1977). In the mid-'sixties the death rate from asthma was even higher, particularly in the 10–14 age group (Speizer *et al.*, 1968a). In the subsequent analysis of events leading up to asthma deaths in young people (Speizer *et al.*, 1968b; Fraser *et al.*, 1971; Inman and Adelstein, 1969) 80% of such deaths were considered to have been 'sudden and unexpected'. In 39% the severity of the terminal attack had not been appreciated by doctors or relatives, and many children had not received corticosteroids during the attack. In a study of deaths from asthma outside hospital between 1963 and 1974 (Macdonald *et al.*, 1976) the associated factors were similar. In addition, several patients had died within a week of discharge from hospital after being treated for severe asthma, and it was suggested that physiological and blood-gas abnormalities had not resolved before their discharge.

In an examination of possible reasons for the recent increase in hospital admission rate for acute asthma in children (Department of Health and Social Security, and Office of Population Censuses and Surveys), Anderson (1978) suggested that there might have been not only a change in morbidity but also a change in criteria for admission.

The purpose of the present study was to examine the factors leading up to the admission of children in status asthmaticus, to determine the severity of the attack, and to try to provide guidelines for management and admission policy.

Patients

During the period from 1 September 1976 to 31 August 1977, 50 children (29 boys and 21 girls) were admitted to this hospital on 72 occasions in status asthmaticus. This was defined as an acute wheezy episode not responding to two doses of bronchodilator 4 hours apart, given either at home or after arrival at hospital. 37 were admitted once, 9 on two occasions, 3 on three occasions, and 1 on eight occasions. This last child will be discussed separately. Therefore, 64 admissions will be considered.

As there is a specialist asthma clinic at the hospital to which children are referred from outside the district, the population from which the admissions were drawn may not have been representative of that served by the average district hospital. Table 1 gives the ages and treatment categories and locality of the children, both those attending the clinic and those admitted to hospital during the period of the study. The children in outpatients were managed as described by Godfrey (1977). For the clinic group, if a child had changed his treatment during the year he

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Table 1 *Percentage of children attending asthma clinic and percentage admitted in status asthmaticus during one year*

Patients	*Clinic (n=289)*	*Admitted (n=50 on 72 occasions)*
Male:female ratio	6:4	5·5:4
Ages (years)		
<1	1	4
1– 4	15	22
5– 9	50	36
10–14	31	34
15, 16	3	4
Treatment category		
Intermittent bronchodilators	32	32
Disodium cromoglycate	29	24
Theophylline	17	8
Beclomethasone	21	20
Corticosteroids on alternate days	1	4
No treatment	—	12
Local	74	68*
Not local	26	32†

*10 of these children did not attend the clinic. †3 of these children did not attend any hospital clinic and 5 were known severe asthmatics attending clinics outside the area.

was classified according to the treatment he was receiving at the end of the study. For the admission group, if a child was admitted more than once he was classified according to the treatment he was receiving before his first admission. Parents were advised to seek the help of their general practitioner, bring the child to casualty, or telephone the hospital if the child's wheezing did not respond to his usual bronchodilator.

Methods

Assessment of severity and investigations. At the time of admission, the house officer recorded details of events leading to admission, including possible precipitating factors, number of previous hospital admissions, and current maintenance treatment. The length of the attack was taken from the time the child started to cough or wheeze until the time of admission. Details of physical examination including measurement of pulsus paradoxicus and investigations performed at the time of admission were also recorded. Each child was given a score for respiratory distress—the clinical score (Table 2). This is a modification of the pulmonary index score of Dabbous *et al.* (1966). The investigations, performed on admission whenever possible, were blood–gas analysis, peak expiratory flow rate (PEFR) measurement, and chest *x*-ray; nasopharyngeal swabs for viral culture and serum for respiratory viral titres were also collected. A specimen of convalescent serum was collected if possible 10–20 days later. Blood was taken for theophylline measurement if the child had received any theophylline compound.

Table 2 *Clinical score*

	Score			
	0	*1*	*2*	*3*
Wheeze	0	Expiratory	Inspiratory and expiratory	Audible without stethoscope or absent
Hyperinflation	0	+	++	+++
Use of accessory muscles	0	+	++	+++

Initial treatment. The patients were assigned one of two treatment regimens according to the severity of illness on admission. Children who met one criterion listed in Table 3 were given the intravenous regimen; otherwise they received the oral one.

Oral regimen

This consisted of prednisolone 2 mg/kg per day in two divided doses and salbutamol inhalations 2·5 mg of respirator solution in 3 ml saline every 4 hours. Salbutamol was given via a Wright's nebuliser with a flow of oxygen of 8 l/min from a wall supply. Those children who were already taking theophylline preparations continued to take them. If the symptoms or PEFR had not improved in 1–2 hours after admission, treatment with the intravenous regimen was started.

Intravenous regimen

The fluids and the intravenous drug dosages are given in Table 3.

All children received IV boluses and infusions of hydrocortisone and aminophylline. Salbutamol was given either intravenously or via a Wright's nebuliser every 4 hours. The order in which each child received

Table 3 *Intravenous regimen*

Criteria for treatment	Dehydration PaO_2 <8 kPa $PaCO_2$ >5 kPa PEFR unrecordable on Wright's peak flow meter
Fluids	Dextrose 4%, saline 0·18%, 70–120 ml/kg per 24 hours
Drug boluses	Hydrocortisone 2 mg/kg +Aminophylline 6* mg/kg over 5 minutes + either salbutamol 5 × 10^{-3} mg/kg over 5 minutes or nebulised salbutamol 2·5 mg respirator solution in 3 ml saline
Drug infusions	Hydrocortisone 1 mg/kg per hour + Aminophylline 1 mg/kg per hour + either salbutamol 5 × 10^{-3} mg/kg per hour or nebulised salbutamol 2·5 mg respirator solution in 3 ml every 4 hours

*At first aminophylline was given as a bolus of 4 mg/kg and an infusion of 0·7 mg/kg per hour. The dose was increased as serum theophylline concentration after 2 hours' treatment was consistently below the optimum therapeutic range (10–20 µg/ml).

the drugs and the route of administration of salbutamol was random as another trial was in progress to compare the effects of these drugs. This did not affect the results discussed in this paper and will be reported separately. The dose of aminophylline was modified in those children who had recently received a theophylline preparation (McKenzie *et al.*, 1978). Serum theophylline was measured 2 hours after the infusion was started and the rate of infusion was altered if this did not come between 10 and 20 μg/ml.

Antibiotics were given if the child had a fever and signs consistent with infection in the chest *x*-ray taken on admission. Oxygen was given by face mask to any child who was hypoxic and blood-gas analysis was repeated if there was no clinical improvement or improvement in PEFR after 4 hours of treatment.

Recovery phase. Once dehydration had been corrected and the PEFR had shown a sustained improvement to 30% of expected for height, IV treatment was replaced by oral prednisolone and nebulised salbutamol. Each child was considered fit for discharge when the PEFR was sustained at 75% or more of expected for height or, for children too young to use a peak flow meter, when wheezing, recession, and tachypnoea were absent. Prednisolone was then reduced over 3 or 4 days. Drug treatment was reviewed before discharge and altered if necessary and the children were regularly followed up in the outpatient clinic.

Statistics. The statistical method used for analysis of results was χ^2 test with Yates's correction for discontinuity.

Results

Age, sex, previous treatment. When compared with the overall population of children attending the outpatient asthma clinic (Table 1) there was no significant difference in the ages, sexes, or proportions of children admitted from the various treatment categories.

Month of admission. The admission rate each month was similar throughout the year. There were 33 admissions between April and September and 31 between October and March.

Mode of admission. Most (60%) children were admitted after being brought to casualty by their parents, some (20%) first saw their general practitioners, and the rest came either directly from the asthma clinic (11%) or from other hospitals (9%). 70% of admissions were clinic attenders and two-thirds of these came directly to casualty.

Previous admissions. 18% of children had never been in hospital before, 36% had had no admissions in the previous year, 32% had had one or two admissions, and 14% had more than two admissions in the previous year.

Precipitating factors. Seven admissions followed an emotional upset at school or at home and 2 followed physical exercise. Three children had been participating in a drug trial and were admitted during the period they were receiving a placebo. One child had erythema multiforme. The precipitating factors for the rest of the admissions could not be defined at the time the children arrived at hospital.

Drugs in the 12 hours before admission. Seven children had had no drugs before admission. Six were undiagnosed asthmatics and one had run out of bronchodilators. The 6 children referred from other hospitals were receiving aminophylline and hydrocortisone, but the theophylline levels on admission in these children were without exception below the lower limit of the accepted therapeutic range (10–20 μg/ml). Either orciprenaline, subcutaneous adrenaline, terbutaline, or aminophylline by suppository had been given to each of 4 other children. The remaining children all had had 1–4 doses of salbutamol in addition to whatever other daily treatment they were receiving, either cromoglycate, beclomethasone, theophylline, or corticosteroids.

Severity of attack on admission. Arterial blood-gases were measured in 38 admissions, 9 of whom were breathing increased fractional inspired oxygen (F_{IO_2}). PEFR measurements were made in 53 admissions. The relationships between the Pa_{O_2} measurements breathing air, the Pa_{CO_2} measurements, the PEFR measurements, and the clinical score are shown in Table 4.

There was no correlation between the magnitude of Pa_{O_2} breathing air and the clinical score. All children with Pa_{CO_2} measurements of $>6\cdot0$ kPa (>45 mmHg) had clinical scores of at least 6 compared with 22 of 30 with Pa_{CO_2} measurements of $<6\cdot0$ kPa ($\chi^2 = 4\cdot5$; $P<0\cdot05$). 13 of 24 children under 5 years and 25 of those older than 5 years had blood-gas analyses ($\chi^2 = 0\cdot43$; P = NS). Of those in whom measurements were taken, the younger group had higher Pa_{CO_2} values (Table 5). Children with pulsus paradoxicus of >25 mmHg tended to have Pa_{CO_2} values >5 kPa ($>37\cdot6$ mmHg) (Table 6) although this did not reach significance. Ten of 11 children who had PEFR measurements of $>25\%$ expected for height had clinical scores of 5 or less compared with only 6 of 42 with PEFR measurements $<25\%$ expected ($\chi^2 = 20\cdot8$; $P = <0\cdot001$).

Table 4 *Blood-gases, PEFR measurements, and clinical score on admission*

	Clinical score		
	Good (*<3*)	*Moderate* (*4–7*)	*Severe* (*>8*)
PEFR (P/min)			
Unrecordable	0	18	6
<25% expected	0	14	4
>25% expected	4	7	0
Too young to blow	2	8	1
Pao_2 in air			
<5·4	0	1	0
5·5–7·9	0	7	2
>8·0	1	15	3
$Paco_2$ (kPa)			
>7·6		1	2
6·1–7·5		2	3
5·1–6·0		11	2
<5	1	14	2
Blood-gases not analysed	5	19	2

Conversion SI to traditional units—Pao_2 and $Paco_2$: 1 kPa≈7·5 mmHg.

Table 5 *$Paco_2$ and age*

$Paco_2$ (kPa)	*Age (years)*	
	<5	*>5*
5·0 or less	2	16
>5·0	11	9

$\chi^2 = 20\cdot3$ P = <0·001

Table 6 *$Paco_2$ and pulsus paradoxicus*

$Paco_2$ (kPa)	*Pulsus paradoxicus (mmHg)*	
	<25	*>25*
5·0 or less	6	1
>5·0	8	11

$\chi^2 = 2\cdot36$ P = NS

There was no correlation between the length of symptoms before admission and $Paco_2$ or PEFR on admission.

Chest x-rays and viral studies. 53 admissions had chest *x*-rays taken and these were considered normal in 9. 28 had evidence of hyperinflation, 2 showed mediastinal emphysema, and 14 showed areas of abnormal shadowing. The presence of mediastinal emphysema did not influence the management and in neither child did it become worse although one child required intermittent positive pressure ventilation (IPPV).

Nasopharyngeal swabs for viral culture were collected from 37 admissions. Respiratory syncytial virus (RSV) was grown from one. Complement-fixation titres against respiratory viruses and *Mycoplasma pneumoniae* were measured in paired sera in 31 admissions. Three showed at least a 2-dilution rise in titre to RSV (the positive culture was from one of these) and 2 children had a similar rise to *Mycoplasma pneumoniae*. All 5 children had abnormal shadows on chest *x*-rays.

Response to treatment. 18 admissions admitted received the oral regimen of prednisolone and nebulised salbutamol. They included all 11 in whom the admission PEFR was >25% expected for height and 2 others who had recordable PEFRs of 15 and 20% expected. Five other children in this group were too young to use the peak flow meter but 4 of them had clinical scores of <5 and the other had normal blood-gases.

The intravenous regimen was given to 46 admissions. This was continued for <12 hours in 12, 12–24 hours in 21, and >24 hours in 8. 14 children received either ampicillin or erythromycin. The time taken to be fit for discharge is shown in Table 7. Two children were discharged before their PEFR measurements were satisfactory and one returned 6 days later with continued wheezing. Most (73%) children were fit for discharge in 4 days or less.

There was no statistical correlation between either the length of symptoms before admission, the admission $Paco_2$ or the admission PEFR, and the time it took to be fit for discharge. 11 of 15 children with abnormal admission chest *x*-rays took at least 4 days to be fit for discharge compared with 7 of 37 with normal or hyperinflated chest *x*-rays ($\chi^2 = 11\cdot7$; P = <0·001). (The other child who had an abnormal chest *x*-ray was discharged before his PEFR was satisfactory.)

One child required IPPV. He had been transferred from another hospital where he had had a rising Pco_2 over 24 hours. The main difference in treatment was that he had not received aminophylline until just before transfer. The Pco_2 on admission to this hospital was 9·6 kPa (72 mmHg). An initial fall in Pco_2 was not sustained and IPPV was necessary for 40 hours. He made an uneventful recovery. No other child was shown to have a rise in $Paco_2$ after admission.

The child who was admitted on 8 occasions was a 13-year-old boy who until the summer before the period of this study had been fairly well controlled at boarding school on beclomethasone. After the

Table 7 *Time to be 'fit for discharge'*

Days	**Peak flow reached 75% expected*	*Children too young to use peak flow meter*
<4	42	5
5–7	9	4
>7		2

*Two children discharged before PEFR 75% expected.

holidays he did not want to return to school and remained at home. He was admitted on each occasion with a Pco$_2$ of >7 kPa ($>52 \cdot 6$ mmHg) but he always responded rapidly to the intravenous regimen. It was, however, known that his early morning PEFR was often low in spite of receiving adequate doses of theophylline, corticosteroids every other day, and salbutamol. In spite of supervision this boy was never satisfactorily controlled and he did not return to boarding school. After the study had ended, he arrived dead in casualty one morning after an acute attack of about 9 hours' duration.

Complications of therapy. One child suffered tremulousness after nebulised salbutamol. Five children became nauseated for about 30 minutes after the bolus dose of aminophylline. Injection of salbutamol intravenously was in most cases followed by a sustained mean increase in heart rate above that measured at the time of admission of 5–10 beats/min.

Change of outpatient drug regimen. After reviewing management, the outpatient treatment was changed before discharge in 34 instances either from intermittent bronchodilator therapy to continuous theophylline or cromoglycate, or from theophylline or cromoglycate to beclomethasone.

Follow-up. Of the 50 children studied, 48 were available for review 6 months after their first admission during the period of the study. 34 had no further admissions and were well controlled. Seven children had had one further admission, 6 children had had 2 further admissions, and one child (the boy described above) had had 8 admissions during the year of the study. Of these 14 who were readmitted, 5 were known to comply poorly with treatment at home and one was subsequently shown to have aspergillosis.

Discussion

After the epidemic of deaths from asthma during the 'sixties (Speizer *et al.*, 1968a, b; Inman and Adelstein, 1969; Fraser *et al.*, 1971) there was an acute awareness of the need for earlier recognition and more aggressive treatment of acute severe asthma. Crompton and Grant (1975) emphasised the need for prompt admission to hospital for asthmatics, and an emergency service was set up in Edinburgh for this. The Hammersmith Hospital has operated an open admission policy for asthmatic children for several years. Parents are advised to seek medical help early if their child becomes acutely wheezy. Most children in this study were clinic attenders and many either had come straight to casualty, often after a phone-call to the hospital, or had made an emergency appointment at the clinic from where they were admitted. The criterion for admission to hospital was the failure to respond to two doses of bronchodilator 4 hours apart, and this may seem to be a low threshold. Nevertheless at least one-third of the 64 children had admission Pco$_2$ measurements of >5 kPa and in 24 of 53 admissions who could use a peak flow meter the measurement was unrecordably low. We think that our criterion for the diagnosis of 'status asthmaticus', and hence admission to hospital, was reasonable.

There was no seasonal variation in admission rate and children belonging to different treatment categories were just as likely to have an acute episode. Most admissions were within the first 48 hours of the start of cough or wheeze but there were a significant number who waited longer before seeking help. The deaths of young asthmatics are thought to be 'sudden and unexpected' (Speizer *et al.*, 1968b). This study shows that the blood–gas analyses and PEFR measurements on children admitted early in their attack are not much different from those admitted later. It may be argued that had an open admission policy not been in operation the early admissions may have stayed longer at home with a less favourable outcome.

The precipitating factor for each admission was difficult to evaluate. Only 16% of children investigated were shown to have an associated viral or mycoplasmal infection. Mitchell *et al.* (1976) found a similar incidence of serological evidence of viral infection in a group of children with wheezy bronchitis and asthma but had more success in isolating the viruses. The methods for collecting and transporting swabs in this study may not always have been satisfactory.

The relationship between the clinical score and the admission Pco$_2$ was barely significant and neither was the presence of pulsus paradoxicus helpful in predicting hypercapnoea. We suggest therefore that, in all but the slightest attacks, the measurement of arterial blood–gases is the only satisfactory method to assess the severity of physiological disturbance in status asthmaticus. Commey and Levison (1976) suggested that sternocleidomastoid contraction and supraclavicular recession are useful signs of severity but their absence does not mean that severe airways obstruction is not present. Similarly, although Galant *et al.* (1978) were able to relate the magnitude of pulsus paradoxicus to other parameters of respiratory function, such as PEFR, the absence of large paradox did not mean that severe airways obstruction did not exist.

Young children were much more severely ill on admission as judged by blood–gas analysis than

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older ones. Six of 8 deaths reported by Buranakul *et al.* (1974) were in children aged 3 years or less and 6 of 13 children in respiratory failure reported by Simons *et al.* (1977) were under age 3 years. Particular attention should therefore be paid to the evaluation of status asthmaticus in young children.

PEFR measurements are useful in following progress after admission to hospital and, in this study, the admission PEFR was also useful in predicting those children who were likely to respond favourably to oral corticosteroids and nebulised salbutamol alone. It may be that those children who can record a PEFR of >25% expected for height could be satisfactorily managed at home either after nebulised salbutamol given in casualty or IM salbutamol given at home together with a short course of prednisolone.

The treatment outlined in this paper resulted in a rapid and sustained improvement in PEFR and was relatively free from side effects. Most children were fit for discharge and return to school within 4 days. Only one child needed IPPV. No other child had a rise in Pco_2, not even those receiving increased F_Io_2. Children with abnormal chest *x*-rays took longer to recover and all five with proved viral or mycoplasma infection took over 4 days to recover. We suggest that if an antibiotic is to be used in asthmatic children, erythromycin is a suitable choice as it will treat *Mycoplasma pneumoniae* and many of the bacteria pathogenic to the respiratory tract.

Gregg (1975) stated that 'Every attack of severe asthma should be regarded as a failure in (his) previous medical care . . .'. In this study over half the children required a change in treatment after their outpatient control had been reviewed. This emphasises the need for regular follow-up of all childhood asthmatics and the need to educate parents to seek help if their children's symptoms increase in frequency.

We suggest that all children presenting in status asthmaticus with a PEFR of <25% expected for height should be admitted to hospital and should be treated with IV aminophylline and hydrocortisone in addition to nebulised salbutamol. They should be considered fit for discharge when PEFR measurements are sustained at 75% expected for height. Young children should, of course, be accompanied by an adult. This practice may not only reduce the mortality due to asthma but also the need for IPPV and will ensure a rapid return to school and normal activity.

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Role of viruses and bacteria in acute wheezy bronchitis in childhood: a study of sputum

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SUMMARY Sputum, nasal swabs, and throat swabs were obtained from 22 children aged between 5 and 15 years during 72 attacks of wheezy bronchitis. A virus, most commonly a rhinovirus, was isolated in 49% of all episodes and in 64% of 22 severe episodes requiring treatment with corticosteroids; the isolation rate was higher early in the illness than later. Virus was recovered more often from sputum than from the nose or throat, suggesting that viral replication occurs freely in the lower respiratory tract: the cytological findings in sputum were compatible with an inflammatory response to viral infection. Pathogenic bacteria appeared to play a minor role compared with viruses, and routine antibiotic treatment was probably of little value in most cases. The significance of the results is discussed in relation to the pathogenesis of childhood wheezy bronchitis.

Wheezy bronchitis of childhood may be defined as an acute illness usually preceded by upper respiratory symptoms and characterised by cough and variable degrees of wheezing, breathlessness, and mucus expectoration. On auscultation high-pitched wheeze is audible over most parts of the chest in addition to medium crepitations or rhonchi. Various terms such as 'asthmatic bronchitis', 'exacerbations of asthma', or 'bronchitis with bronchospasm' have been used to describe this illness. Several studies have established that during these episodes common respiratory viruses can be isolated from the upper respiratory tract (McIntosh *et al.*, 1973; Minor *et al.*, 1974; Horn *et al.*, 1975; Mitchell *et al.*, 1976). Horn and Gregg (1973) and Horn *et al.* (1979) noted that certain children experience recurrent episodes of wheezy bronchitis and it seems clear that undetermined constitutional factors must influence the individual child's response to infection with common respiratory viruses. The pathogenic mechanisms underlying the cough, bronchoconstriction, and excess lower respiratory secretion that characterise this condition are unknown. It is possible either that the lower respiratory symptoms are a remote response to viral infection in the upper respiratory tract, or that they are a consequence of viral invasion of the bronchial mucosa.

We now describe a study designed to provide further evidence on this point. Sputum collected from children during attacks of wheezy bronchitis was examined in parallel with nasal and throat swabs using virological, bacteriological, and cytological techniques.

Patients and methods

Clinical methods. The study was carried out in a special asthma and bronchitis clinic held twice weekly for children in a general practice. Between October 1974 and April 1976 (excluding July and August 1975) each child attending for treatment of an episode of wheezy bronchitis, as defined above, was accepted for study provided he presented within 5 days of onset of the initial symptoms (upper or lower respiratory) and was able to expectorate sputum. 22 children (15 boys and 7 girls), aged between 5 and 15 years, satisfied these conditions; all had a history of recurrent wheezy bronchitis and were among those previously investigated by Horn *et al.* (1975). The number of episodes investigated per child ranged from one to 15. 19 of the 22 children wheezed on exercise, on exposure to inhaled allergens, or with emotional upsets; the remaining 3 wheezed only during attacks of wheezy bronchitis. 17 of the 22 children gave positive reactions to at

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least one of 14 inhaled allergens used in skin prick tests. These children were defined as atopic and the remaining 5 as nonatopic; 3 of the nonatopic children were known to wheeze only during attacks of wheezy bronchitis. A family history of asthma or allergic rhinitis was present in 12 atopic children and 5 nonatopic ones; the remaining 5 children had no such family history but were atopic on prick testing.

Episodes were classified retrospectively according to severity on the basis of airflow obstruction and the need to give corticosteroids, judged clinically. Airflow obstruction was measured by the fall in peak expiratory flow (PEF) rate, expressed as a percentage of the predicted PEF for height (Godfrey *et al.*, 1970). Episodes were classified as severe if treatment with corticosteroids was required for control or if the fall in PEF was at least 60%; moderate episodes were those which did not require corticosteroids and in which PEF fell by 40–59%; mild episodes were those in which the PEF fell by less than 40%.

Appropriate bronchodilator or corticosteroid treatment was prescribed during the acute phase of the illness until prophylaxis with an oral bronchodilator and sodium cromoglycate or beclomethasone dipropionate aerosol could be resumed. Physiotherapy was an integral part of treatment and sputum samples were obtained by encouraging coughing during postural drainage and percussion.

As controls, 31 nasal and throat swabs collected from 17 children between acute attacks were also examined virologically, but control sputum samples could not be obtained.

The first sputum samples, nasal swabs, and throat swabs examined in each episode were collected at the child's first attendance, within 5 days of onset of respiratory symptoms, and before prescribing antibiotics or corticosteroids. Whenever possible a second nasal swab and sputum sample were obtained later in the illness, generally within 5 days of the first. If bacterial infection was thought likely on clinical grounds, penicillin, co-trimoxazole, or ampicillin (in order of frequency) was prescribed when the child first attended the clinic. One of these was prescribed at the second visit, after second samples had been collected, if the first samples had shown *Streptococcus pyogenes* in the throat or if there had been any pathogenic bacteria in the sputum and the clinical condition still warranted treatment.

Specimens for virological examination were kept chilled in transport medium and delivered to the laboratory within 4 hours. Throat swabs transported in Stewart's medium and sputum samples were examined bacteriologically, and the sputum was also examined cytologically.

Laboratory methods. The techniques for isolating viruses and *Mycoplasma pneumoniae* were as previously described (Horn *et al.*, 1975), except that MRC-5 human embryo lung fibroblasts were substituted for WI-38 cells which were no longer obtainable. After inoculation into standard cultures, the remainder of each specimen was stored at -70°C and later cultured in rhinovirus-sensitive HeLa cells (Strizova *et al.*, 1974). Rhinoviruses were characterised by their typical cytopathic effect (cpe) and by their acid lability, but were not serotyped. No attempt was made to quantitate rhinovirus by titration, but the relative amount of virus present in the various types of specimens was assessed roughly by noting the day of development of rhinovirus cpe in the culture and calculating the means for nasal swabs and sputum samples. Organ cultures or other special techniques for isolation of coronaviruses were not used.

Throat swabs were cultured on blood agar and MacConkey agar incubated aerobically at 37°C. Sputum was homogenised with pancreatin, shaken, and similarly cultured undiluted, and at a dilution of 10^{-4}. Isolations of *Streptococcus pneumoniae* and *Haemophilus influenzae* were considered significant if the organisms were detected at a dilution of 10^{-4}: *Staphylococcus aureus* and *S. pyogenes* in any numbers were considered significant.

Sputum smears were stained with haematoxylin and carbol chromotrope 2R. The whole area of each specimen was examined by a single observer, and the prevalence of leucocytes, bronchial epithelial cells, and macrophages was estimated on an arbitrary scale 1+ to 3+. Eosinophils were assessed as an approximated percentage of the total cellular content: an arbitrary figure of at least 25% eosinophilia was considered abnormal, as were bronchial epithelial cells or macrophages scored as 1+ or more and leucocytes as 2+ or more.

Results

72 episodes of wheezy bronchitis were studied, of which 18 were classified as mild, 24 as moderate, and 30 as severe. Upper respiratory symptoms were present in all but one moderately severe episode. Rhinorrhoea was present in 71 episodes, pharyngitis in 39, otitis media in 2, sinusitis in 2, pyrexia in 11, headache in 8, and myalgia in 2. Sputum samples were obtained at the first attendance in all but 2 episodes in which severe bronchospasm prevented expectoration; in these 2, sputum was obtained at the second attendance. In a few episodes nasal or throat swabs could not be obtained. Second samples were obtained in 54 episodes: 42 within 5 days of the first, 11 within 8 days, and one after 15 days.

Virology. One or more viruses were isolated in 35 (49%) of the 72 episodes. The virus isolation rates in mild, moderate, and severe episodes were 17, 54, and 63% respectively, and in 22 severe episodes requiring corticosteroid treatment the recovery rate was 64%. Table 1 shows the number of episodes yielding virus, with its source, and the Figure gives the rate of virus isolation for each category of specimen. Rhinoviruses predominated over all other agents and were recovered throughout the study. Influenza viruses were isolated only during the two main epidemic periods, December 1974 to January 1975 (influenza A), and January to March 1976 (influenza A and B). Of the 30 severe episodes investigated, 12 were associated with rhinovirus alone or in combination with another agent, and 4 with influenza viruses.

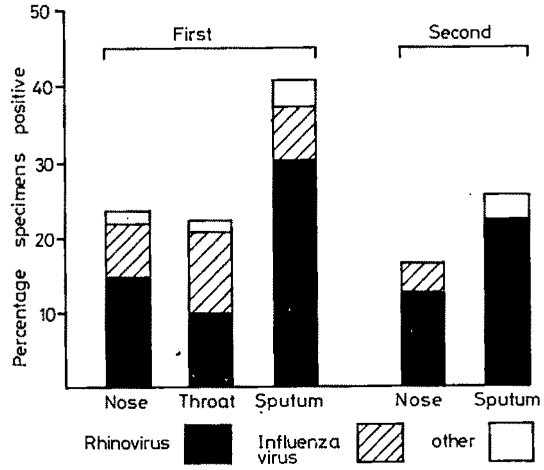

Figure *Rates of isolation of rhinovirus, influenza virus, and other viruses (including M. pneumoniae) from various specimens.*

The first sputum samples were the best source of virus, particularly rhinovirus: influenza viruses were more common in nasal and throat swabs than in sputum (Figure). 29 (41%) isolates were obtained from 70 first sputum samples, 15 (23%) from 64 first nasal swabs, and 14 (22%) from 64 throat swabs. The overall isolation rate from first sputum samples was therefore significantly higher than from the first nasal or throat swabs ($P<0\cdot05$, χ^2 test). The mean day of development of rhinovirus cpe in HeLa cells was 3·9 days for first sputum samples and 4·6 days for first nasal swabs, and in MRC-5 cells the corresponding figures were 5·1 and 8·0 days, indicating that the sputum probably contained more virus than the nasal swabs. The second samples, taken later in the illness, gave fewer isolates than the first, but again sputum showed more isolates than the nose. In only 3 episodes were second samples positive when first samples had been negative.

Only one of the 31 control swabs from the upper respiratory tract contained virus.

Bacteriology. 28 (39%) of the 72 episodes showed significant bacterial isolations but, in 15 of these, the isolations were from throat swabs; only 3 sputum samples contained the same organism as was found in the throat swab. Only 12 (17%) of 70 first sputum samples gave significant bacterial isolations (Table 2), and the episodes from which these samples were obtained were not distinguishable by any particular clinical feature. The bacteria isolated from sputum in 6 virus-positive episodes

Table 1 *Isolation of viruses and M. pneumoniae from nasal swabs, throat swabs, and sputa collected during 72 episodes of wheezy bronchitis*

	Total no. of episodes from which agents were isolated	*Episodes in which an agent was isolated*							
		From 1st sample				*From 2nd sample*			
		URT only	*Sputum only*	*URT and sputum*	*Total*	*URT only*	*Sputum only*	*URT and sputum*	*Total*
Rhinovirus	20	3	7	10	20	2	8	2	12
Influenza A	6	2	0	3	5	1	0	0	1*
Influenza B	1	0	0	1	1	0	0	0	0
Parainfluenza 1	2	0	0	1	1	0	1	0	1*
Respiratory syncytial virus	1	0	1	0	1	0	0	0	0
Adenovirus	1	0	0	0	0	0	1	0	1*
Influenza A + rhinovirus	2	0	2Rh	1IA	2	1IA	0	0	1
Parainfluenza 3 + rhinovirus	1	0	1PI3	1Rh	1	0	1Rh	0	1
M. pneumoniae + rhinovirus	1	1Mp	0	1Rh	1	0	0	1Rh	1

*Episodes in which an agent was isolated from 2nd samples but not 1st.
Rh = rhinovirus; IA = influenza A; PI3 = parainfluenza 3; Mp = *Mycoplasma pneumoniae*.

Table 2 *Specimens showing significant isolations of bacteria*

	Throat swab (n=70)		*Sputum samples*			
			1st (n=70)		*2nd (n=53)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
S. aureus	11	(16)	6	(9)	2	(4)
S. pyogenes	8	(11)	1	(1)	0	(0)
S. pneumoniae	0	(0)	3	(4)	1	(2)
H. influenzae	0	(0)	2	(3)	0	(0)
Total	19	(27)	12	(17)	3	(6)

were similar to those recovered in 7 virus-negative episodes. There was no clear association between individual viruses and bacteria except perhaps in the case of influenza virus; in 3 of the 7 episodes in which influenza was the only virus found, bacteria were present in sputum (*S. aureus* twice and *S. pneumoniae* once), compared with isolation of bacteria from sputum in only 3 out of 20 episodes showing rhinovirus (*S. aureus*, *H. influenzae*, and *S. pneumoniae*, each once). There was no clear correlation between the bacterial isolation rate from first sputum specimens and the severity of illness, the rates in mild, moderate, and severe episodes being respectively 1 (6%) of 18, 7 (29%) of 24, and 4 (13%) of 30. In 38 episodes in which pharyngitis occurred and throat swabs were cultured, 13 (34%) of these swabs showed pathogenic bacteria (*S. pyogenes* 7 times and *S. aureus* 6 times). Seven of the 11 febrile children had bacterial infections. Both cases of sinusitis were associated with *S. pyogenes* and one of the two cases of otitis media showed *S. pneumoniae*.

Antibacterial agents were prescribed at the time of the first visit in 30 episodes but the cultures subsequently showed that bacterial infection had been present in only 9 of these episodes, 5 of the relevant first sputum samples being positive, and 7 of the throat swabs. No initial antibacterial therapy was given in 42 episodes, and only one second sample from these episodes contained bacteria (*S. aureus*) which had not been present in the first sample. Both first and second sputum samples were examined bacteriologically in 50 episodes of which 22 were treated with antibiotics at the time of the first visit and 28 were not. The bacterial isolation rate from first sputum samples was 14% in both the treated and the untreated group. In the second samples the rates fell in both groups, to 5 and 7% respectively.

Cytology. The cells classified as macrophages contained foamy and particulate material and were considered by the cytologist to be alveolar in origin. The relative frequency of the various cell types appeared to be little influenced by the agent isolated (Table 3) and there was no significant correlation between any of the cytological findings and severity. Bronchial epithelial cells in second sputum samples were more common in 'bacteria-positive' than in 'bacteria-negative' episodes, but numbers were small and the differences not significant. Both leucocytosis and eosinophilia graded as significant were less common in second samples than in first, and the decrease in eosinophils occurred both in the presence and absence of corticosteroid treatment. In 48 episodes both first and second sputum samples were examined cytologically. In 21 such episodes initially treated with antibiotics, 81% of first samples showed leucocytosis compared with 33% of second samples (and this difference was significant, $P<0\cdot01$, χ^2 test). In 27 episodes not treated with antibiotics the rates in first and second samples were 74 and 52% respectively ($P>0\cdot05$, χ^2 test).

Table 3 *Percentage of sputum samples showing significant cytological abnormalities in episodes categorised according to the microbiological findings*

Microbiological findings during the episodes	*No. of samples examined*	% of sputum samples showing an abnormal content* of indicated cell types: *Bronchial epithelial cells*	*Macrophages*	*Leucocytes*	*Eosinophils*
Virus-positive† (n = 35)	1st, 33 2nd, 27	48 44	48 52	82 59	61 30
Virus-negative (n = 37)	1st, 37 2nd, 23	43 39	54 70	76 26	59 43
Bacteria in sputum‡ (n= 13)	1st, 13 2nd, 7	54 71	38 43	85 57	62 14
No bacteria in sputum (n= 59)	1st, 57 2nd, 43	44 37	54 63	77 42	60 40

*Defined in Methods, †virus recovered from one or more of the specimens originating in the episode, ‡significant isolation of bacteria from either first or second sputum specimen from the episode.

Atopy. 14 episodes in the 5 nonatopic children were compared with 58 in the 17 atopic children. Significant eosinophilia in sputum was less common in the nonatopic children (43% of 14 episodes) than in the atopic group (78% of 58 episodes); the virus isolation rate was higher in the nonatopic (71% of 14 episodes) than in the atopic children (43% of 58 episodes). Both of these differences were significant ($P < 0{\cdot}05$, χ^2 test) although the statistical comparison was somewhat unsatisfactory as one atopic child contributed 9 episodes and one, who was nonatopic, contributed 15. The individual virus isolation rates in these 2 children were 7 (78%) of 9 episodes in the nonatopic child and 6 (40%) of 15 episodes in the atopic child. The serum immunoglobulin A of each of these children was at the lower limit of the normal range for his age.

Discussion

Eadie *et al.* (1966), Stenhouse (1967), and Stott *et al.* (1968) found that rhinoviruses could be isolated from sputum of bronchitic adults, sometimes in high titre. Lambert and Stern (1972) cultured sputum and nasal and throat swabs from two asthmatic subjects, one of whom was a child, and recovered virus in 5 of 11 exacerbations. In the present study of wheezy bronchitis of childhood a virus was isolated from 49% of episodes, and the sputum samples collected within 5 days of onset of symptoms gave a virus isolation rate of 41%. These figures are probably an underestimate of the true incidence of viral infection as our techniques may have failed to detect some rhinovirus strains, which are particularly difficult to cultivate, as well as coronaviruses. The latter are known to be important in this condition (McIntosh *et al.*, 1973).

In previous studies, Horn *et al.* (1975, 1979) showed that rhinoviruses were the agents most often isolated from the upper respiratory tract during attacks of wheezy bronchitis; in the present study these viruses were found even more commonly in sputum, especially in severe episodes. Although the volume of sputum cultured for virus was probably greater than the volume of nasal secretions, the frequency of isolation of rhinovirus from sputum and the speed with which the cpe developed in the cultures strongly suggested that more virus was present in the lower than in the upper respiratory tract and that its detection in sputum was not simply due to contamination with upper respiratory secretions. As in earlier studies (Horn *et al.*, 1975, 1979) influenza virus was found relatively rarely (in 9 of 72 episodes), although the frequency will naturally depend in part on the epidemic prevalence of influenza at the time of study. It remains uncertain whether influenza viruses have less propensity for causing wheeze than rhinoviruses.

There was little evidence to suggest that bacterial infection was a frequent initiating cause of wheezy bronchitis. Pathogenic bacteria were found in 27% of throat swabs, but the same organisms were rarely found in sputum. The clinical suspicion of bacterial infection raised in a proportion of the episodes by severe pharyngitis, high pyrexia, or otitis media was confirmed by bacteriological tests in about half the cases; secondary bacterial infection was uncommon regardless of antibiotic treatment. The results gave little justification for the use of routine antibacterial treatment in the absence of specific indications, although it was noted that the decrease in leucocytosis in second sputum samples was more pronounced in antibiotic-treated than in untreated episodes.

Our evidence shows that virus infects the lower as well as the upper respiratory tract in many episodes of wheezy bronchitis. The bronchial epithelial cells and inflammatory cells found in sputum confirm that the lower respiratory tract is infected, and the evidence therefore suggests that the bronchoconstriction occurring in wheezy bronchitis is produced by mechanisms initiated locally. It is not known whether rhinovirus infection in normal children extends to the lower airways although the symptoms to which it gives rise are confined to the upper respiratory tract. Direct evidence is impossible to obtain because sputum is not produced by normal children. Indirect evidence suggests that viral invasion may occur in the absence of lower respiratory symptoms, since Cate *et al.* (1973), Fridy *et al.* (1974), Blair *et al.* (1976), and Hall *et al.* (1976) all showed minor abnormalities of peripheral airways function in normal adults with colds. The abnormality of the child who develops wheezy bronchitis during virus infection may therefore be associated not so much with the presence of virus in the lower respiratory tract as with its excessive replication there and the effect of this on his already increased liability to bronchoconstriction. This view is compatible with the findings of Empey *et al.* (1976), who showed that the bronchoconstrictor response to histamine in normal subjects with colds was greater than in those without. These authors suggested that the response of the asthmatic, whose airways epithelial receptors are already sensitised, is an exaggeration of the normal.

Allergic factors may clearly also be relevant to the aetiology of childhood wheezy bronchitis; many of the patients are atopic and the present study shows that viral infection is often associated with sputum eosinophilia. A link between mechanisms of allergy and viral infection, at least in atopic subjects, has been given by Ida *et al.* (1977) who showed that incubation of human leucocytes with virus *in vitro* enhanced their release of histamine when they were subsequently exposed to ragweed antigen or anti-human IgE.

The findings in this study suggest that children subject to wheezy bronchitis may be regarded as abnormal not only in their exaggerated bronchoconstrictor response, but also in the profuseness of viral replication in the lower respiratory tract, with its accompanying inflammatory reaction. The reason for excessive virus growth at this site is not clear but may possibly be related to defects of immunity, such as local IgA deficiency. A study of immunoglobulins in sputum might be profitable when sufficiently standardised techniques become available.

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Changing incidence of neonatal hypermethioninaemia: implications for the detection of homocystinuria

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SUMMARY The Guthrie test was used to measure blood methionine concentrations in 670 764 neonates during the period from May 1970 to December 1977. Raised values (>4 mg/100 ml; 268 μmol/l) were found in 147 babies (6–14 days old) and 55 of these still had raised values when retested 2–6 weeks later. 48 infants had transient hypermethioninaemia of at least 3 weeks' duration, one had a more persistent form associated with abnormal liver function tests, 3 had different forms of homocystinuria, and one infant, who was asymptomatic at the time of detection, had hypermethioninaemia associated with a rapidly fatal form of tyrosinaemia (tyrosinosis). Two infants could not be followed up. Transient hypermethioninaemia has not been detected in this laboratory since 1975. There was a greatly reduced incidence of transient hypermethioninaemia in girls after 1972 and in boys after 1975; this may have been due to recent changes in infant feeding practices in the UK. Homocystinuria was last detected in this laboratory in 1972; the apparent change in incidence is significant ($P<0 \cdot 05$) and suggests that the diagnostic value of this screening procedure should be reassessed.

Neonatal screening for homocystinuria on a national scale is not yet acceptable because of the apparent low incidence of the disease, the uncertainty about the reliability of methods of screening, and about the long-term efficacy of current methods of treatment. Results from different screening centres suggest that the incidence of homocystinuria varies considerably from one area to another, but the extent to which this reflects a true difference in the incidence of the disease or a difference in methodology has been questioned (Thalhammer, 1975; Wilcken and Turner, 1978). Classical homocystinuria can be accompanied by hypermethioninaemia in the neonatal period (Komrower *et al.*, 1966) and this finding forms the basis of one simple screening procedure (Guthrie, 1968). However, hypermethioninaemia does not occur in variant forms of homocystinuria associated with defects in the biosynthesis of folate coenzymes (Mudd *et al.*, 1970, 1972) and may sometimes be absent in classical homocystinuria in the first days of life (Komrower *et al.*, 1966; Levy *et al.*, 1971).

Transient hypermethioninaemia in the neonatal period has been associated with a high protein intake and, in premature infants at least, a low hepatic cystathioninase activity may be a contributory factor (Levy *et al.*, 1969; Sturman *et al.*, 1970). Hypermethioninaemia may also be found in some forms of tyrosinaemia (Scriver *et al.*, 1966), in severe liver disease (Walshe, 1953; Iber *et al.*, 1957), and in association with a deficiency of hepatic S-adenosylmethionine synthetase activity (Gout *et al.*, 1977).

In 1970, the screening programme for phenylketonuria at this hospital was extended to include the detection of homocystinuria in the newborn by measuring blood methionine concentrations. The results of this additional study are presented in this report.

Methods

The sample. Since May 1970 the neonatal screening laboratory at this hospital has screened all babies born in an area corresponding to that now under the

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auspices of the North-east and North-west Thames Regional Health Authorities. When the National Health Service was reorganised in 1974 the area from which patients were drawn changed slightly; small parts of Buckinghamshire and Berkshire were then excluded.

Collection of specimens. On or after the 6th day of life and in most instances up to the 14th day, midwives or health visitors collected blood, obtained by heel prick, on to absorbent cards (supplied by the Department of Health and Social Security; Code no. HMR 101/6) which were then posted to the laboratory in protective plastic covers.

Blood methionine assay. The method was basically that of Guthrie (1968). Dried blood spots of 6·4 mm in diameter were punched out of the cards and placed on the surface of an agar plate containing the inhibitor methionine sulphoximine and spores of *Bacillus subtilis* (strain ATCC-6633). Standard controls which consisted of expired donor bloods containing a range of L-methionine concentrations (1–20 mg/100 ml; 67–1342 μmol/l) were also included on the plate. Plates were incubated overnight at 37°C. The inhibitor suppresses growth of *B. subtilis* unless methionine is present in sufficient concentrations. The methionine concentration in the blood sample was determined by comparing the diameter of the growth zone near the blood spot with that of standard controls.

Other laboratory investigations. Amino-acids were eluted from blood spots with ethanol (70% by vol. in water), separated by thin-layer chromatography and located on separate layers with ninhydrin and iodoplatinate reagents (Ersser and Smith, 1976). Amino-acids in plasma and urine were analysed by both thin-layer and quantitative ion-exchange chromatography (Ersser, 1976).

Results and discussion

Overall findings. During a 7½-year period blood methionine concentrations were determined in 670 764 neonates. Raised values were initially detected in 147 infants and 55 of these still had raised blood methionine levels when retested 2–6 weeks later (Table 1). Of the babies who had abnormal blood methionine concentrations in the 2nd test, 3 had different forms of homocystinuria, one had a severe form of tyrosinaemia (tyrosinosis), one had hypermethioninaemia associated with abnormal liver function tests, and 48 had transient hypermethioninaemia which resolved uneventfully. The other 2 babies were not fully investigated; one went abroad and the other, who had transient hypermethioninaemia without homocystinuria, was admitted to another hospital with severe congenital abnormalities of the central nervous system.

Table 1 *The prevalence of hypermethioninaemia in 670 764 neonates*

Year	*No. screened*	*No. with raised blood methionine concentration (>4 mg/100 ml; >268 μmol/l)*		*Homocystinuria confirmed (n = 3)*	*Transient hypermethioninaemia (n = 48)*
		1st test (n = 147)	*2nd test (n = 55)*		
1970*	67 134	24	6	1	4
1971	103 540	27	15	1	13
1972	96 286	26	17	1	15
1973	91 017	22	5	0	5
1974	82 523	9	7	0	7
1975	77 439	27	4	0	4
1976	76 794	6	1	0	0
1977	76 031	6	0	0	0

*Began 11th May 1970.

Although initial tests were generally done on specimens obtained 6–14 days after birth, some specimens were not entirely satisfactory and repeat samples were needed before an accurate value could be obtained for a suspected abnormal blood methionine concentration. Since 1971, about 5% of all first specimens have been unsatisfactory.

Transient hypermethioninaemia. 48 of the 517 939 babies screened in the period 1970 to 1975 had a transient hypermethioninaemia of at least 3 weeks' duration but this resolved uneventfully in half of them by the 3rd month of life and in all of them by the 5th month. Several of these infants had very high protein intakes and in such cases mothers were advised to change to a milk with a lower protein content. None of the infants with transient hypermethionaemia was known to have been breast fed but our records on this point were unfortunately incomplete. One infant whose blood methionine concentration increased to 1342 μmol/l during a 3-month period was grossly overweight (height, 25th centile; weight, 90th centile); he had been weaned early and was receiving large amounts of protein (protein intake from milk alone was 5 g/kg per day). Appropriate adjustment of his diet was accompanied by a rapid reduction of blood methionine to a normal concentration.

Transient hypermethioninaemia was not detected in the 152 825 neonates screened in 1976 and 1977. There was a striking reduction in the incidence of transient hypermethioninaemia in the girls after 1972 ($P<0\cdot01$) and in the boys after 1975 ($P<0\cdot01$) (Figure). There were no obvious changes in methods of sample collection or analysis which could have

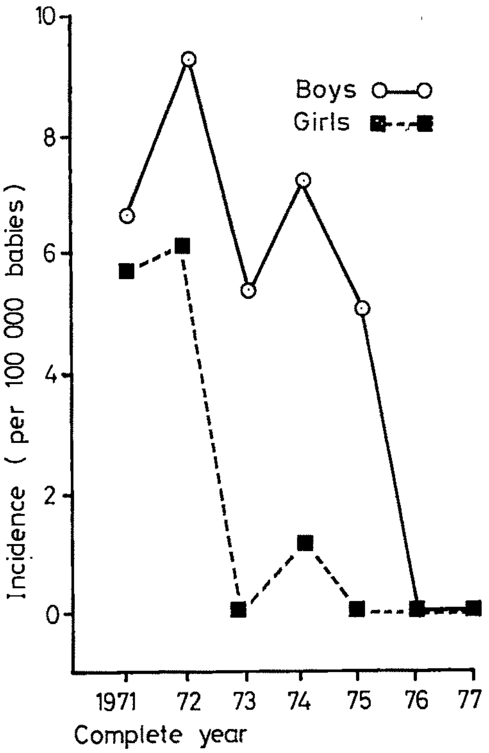

Figure *The incidence of transient hypermethioninaemia in baby boys and girls.*

accounted for this. The most likely explanation is the change in infant feeding practice which has taken place in the UK. A reduction in the protein content of infant milk formulae, later introduction of solids, and a renewal of interest in breast feeding may all have contributed.

The maximum blood methionine concentrations recorded in boys and girls with transient hypermethioninaemia were similar (boys: mean 12 mg/100 ml (805 μmol/l), gross range 5–20 mg/100 ml (336–1342 μmol/l); girls: mean 11 mg/100 ml (738 μmol/l), gross range 7–16 mg/100 ml (459–1072 μmol/l)). These maximum values tended to occur later in girls than in boys (girls: mean 45 days, gross range 21–87; boys: mean 30 days, gross range 6–75) but the difference was not significant. Differences in the periods between sampling in different individuals and the small number of affected infants suggest that this finding should be interpreted with caution.

Homocystinuria. During the first 3 years of the screening programme homocystinuria was confirmed in 3 infants (Table 2) giving an incidence of one in 88 987 during that period. One required treatment with a low methionine diet, one responded to treatment with pyridoxine, and the 3rd had a transient form which responded to a low-protein diet combined with pyridoxine supplement, and resolved within a year so that no further treatment was required. Table 2 compares the initial blood methionine concentrations in these patients. The infant with the pyridoxine-responsive form had lower initial blood methionine concentrations than the infant who responded only to diet. Levy *et al.* (1971) observed that an infant with the pyridoxine-responsive form had a normal blood methionine concentration at 4 days. Brenton and Cusworth (1971) found that clinical manifestations were less severe in the pyridoxine-responsive form.

No further cases of homocystinuria have been detected here since 1972; the change in incidence between the periods 1970–72 and 1973–77 is significant ($P<0\cdot05$).

Other conditions which were associated with hypermethioninaemia. A baby boy who was asymptomatic at the time of detection had hypermethioninaemia associated with an acute form of tyrosinaemia (tyrosinosis). The blood methionine concentration was only slightly raised at 6 days but had increased further by 3 weeks. Further investigations showed the presence of tyrosinaemia, tyrosyluria, and a proximal renal tubular defect. Failure to thrive, liver dysfunction, and defective blood coagulation soon became evident and despite attempts to control blood methionine and tyrosine concentrations the child died at 14 weeks. Gjessing and Halvorsen (1965) and Larochelle *et al.* (1967) concluded that the hypermethioninaemia which occurs in acute tyrosinosis is due to severe liver damage, but this was contested by Gaull *et al.* (1968) who suggested that an unidentified abnormality caused both the hypermethioninaemia and the tyrosinaemia. Linblad *et al.* (1977) suggested that some severe forms of hereditary tyrosinaemia may be associated with a fumarylacetoacetase deficiency and that the resulting metabolites, succinyl acetate and succinylacetone, are toxic to the liver and kidneys.

Another baby boy, born in 1970, had a raised blood methionine concentration (about 10 mg/100 ml; 671 μmol/l) and raised serum alkaline phosphatase, alanine transferase, and aspartate transferase activities which persisted into the 2nd year of life. No other biochemical abnormality was detected and unlike the otherwise similarly affected infants described by Komrower and Robins (1969) he was not anaemic. The child developed normally and the condition resolved spontaneously without treatment or change of diet.

Table 2 *Summary of findings in three patients with homocystinuria and a patient with a severe form of tyrosinosis*

Disease	*Sex*	*Year of detection*	*Blood methionine concentrations mg/100 ml (μmol/l)*		*Other laboratory findings*	*Treatment and outcome*
			Age (6–7 days)	*Age (3–4 weeks)*		
Homocystinuria responding only to diet	M	1970	20 (1342)	20 (1342)	*3 weeks* Plasma homocystine 0·25–0·5 mg/100 ml. Urine analysis: positive cyanide-nitroprusside test. Increased excretion of homocystine	*8 weeks* No response to pyridoxine. Biochemical response to low methionine diet *8 years* Clinically normal. Controlled by low methionine diet
Homocystinuria pyridoxine responsive	M	1971	12–15 (805–1007)	15 (1007)	*3 months* Plasma methionine >20 mg/100 ml, homocystine 0·78 mg/100 ml Urine analysis: weakly positive cyanide-nitroprusside test. Increased excretion of homocystine	*3 months* Responded to low protein diet. *6 months* Responded to pyridoxine 250 mg twice daily. *7 years* Controlled with pyridoxine. No clinical manifestations of homocystinuria. History of asthma and chest infections. Cysts in right upper lobe—cause unknown.
Homocystinuria transient	F	1972	10–12 (671–805)	20 (1342)	*6 weeks* Urine analysis: intermittently positive cyanide-nitroprusside test	*8 weeks* Responded to low protein diet and pyridoxine *1 year* Blood methionine normal on normal diet and without pyridoxine supplements *5 years* Clinically and biochemically normal
Tyrosinosis (tyrosinaemia)	M	1976	4 (268)	11 (738)	*3 weeks* Plasma tyrosine 800 μmol/l *5–6 weeks* Serum phosphate 0·88 mmol/l, calcium 2·15 mmol/l, alkaline phosphatase 1079 IU/l. Urine analysis: aminoaciduria (generalised), glucosuria, tyrosyluria. Megaloblastic anaemia. Abnormal clotting function	Treatment with a diet low in methionine, phenylalanine, and tyrosine produced a rapid reduction in plasma tyrosine but raised plasma methionine persisted. The child developed hepatosplenomegaly with ascites and died at 3 months after pulmonary haemorrhage. Early cirrhosis of the liver was present

Discussion and conclusions

During the early years of the neonatal screening programme at this hospital most bottle-fed infants in the UK were receiving cows' milk preparations with a high protein content (giving neonates about 5 g protein/kg per day) and many of these infants were also receiving solid foods by 4 weeks (Black, 1971; Shukla *et al.*, 1972; Davies, 1973). The association of neonatal hypermethioninaemia with a high protein intake had already been recognised (Komrower and Robins, 1969), and Sturman *et al.* (1970) suggested that the high methionine:cystine ratio of the protein in cows' milk was inappropriate for human infants. Reports on the possible harmful effects of infantile overnutrition (Taitz, 1971; Menkes *et al.*, 1972; Shukla *et al.*, 1972) may have influenced such feeding practices as the early introduction of solid foods, and may have contributed to the initial reduction in the incidence of neonatal hypermethioninaemia in 1973. Several 'modified' milks with protein concentrations of 1·8 g per 100 ml were introduced in 1973 and 1974. Also in the period from about 1970 to 1972, maternity units began to use infant milk formulae which were accurately diluted and prepacked by the manufacturers.

The apparent disappearance of transient neonatal hypermethioninaemia in 1976 may have been due to the withdrawal of high-protein milks—such as national dried full cream milk—the widespread introduction of infant milk preparations with a protein content and casein:lactalbumin ratio approaching that of human breast milk, and to the publication *Present-day Practice in Infant Feeding* (Department of Health and Social Security, 1974) which put forward official recommendations for changes in infant feeding practice. The reason why the girls but not the boys responded as early as 1973 is uncertain but could be due to a difference in ability to metabolise methionine or to a difference in total milk intake. Whatever the cause these results suggest that the protein intake, or more specifically the methionine intake, of infants decreased in 1973 and decreased further in 1976.

The apparent failure to detect homocystinuria since 1972 coincided with the reduction in the incidence of neonatal hypermethioninaemia. No 'missed' cases of homocystinuria in the areas concerned have yet been brought to our notice but the disease may not be obvious in the early stages. Thus, it appears that the earlier moves away from breast feeding (Newson and Newson, 1962) and the tendency towards infantile overnutrition were conducive to the detection of homocystinuria by neonatal screening programmes which measured blood methionine concentration in early infancy. Ironically, better infant feeding practices necessitate a reassessment of the methods used to detect homocystinuria. Furthermore possible similar effects on the neonatal screening of other inborn errors of amino-acid metabolism should be borne in mind.

These findings, and the studies of Wilcken and Turner (1978) in New South Wales, suggest that the true rate of homocystinuria is greater than that indicated by neonatal screening programmes. Infants with mild forms of the disease are even less likely to be detected. Estimates of the incidence of homocystinuria have varied widely from one area to another. This could be partly attributed to different methods of screening and to different patterns of infant feeding. At present there is no justification for national screening of homocystinuria early in the neonatal period and the reliability of the Guthrie method needs to be carefully reassessed.

The concentration of methionine in blood is normally <67 μmol/l and the cut-off point of 268 μmol/l used in the screening programme may now be too high. During a trial period, initially for one year, all infants screened at this centre who have blood methionine concentrations of 2 mg/100 ml (134 μmol/l) or more will be further investigated. However, recent experience suggests that this procedure will not improve the detection of homocystinuria. Furthermore, Wilcken and Turner (1978) suggest that even including a test for urinary homocystine in a neonatal screening programme at 6 weeks does not ensure detection of the disease.

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Dr I. B. Sardharwalla of the Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, was invited to comment:

Our own experience is similar to that described by Whiteman *et al.* Most infants in the North-western Region are tested between 10 and 14 days after birth (primarily for phenylketonuria) and to date over half a million babies have been screened. The method used is one-dimensional paper chromatography of plasma (Scriver *et al.*, 1964) which can detect 6 related amino-acid abnormalities, including hypermethioninaemia (Sardharwalla *et al.*, 1972). This technique is sufficiently sensitive to detect a plasma methionine concentration of 0·2 mmol/l (2·98 mg/100 ml). If plasma methionine concentration is >0·6 mmol/l (>8·9 mg/100 ml) immediate steps are taken to have the baby brought to the metabolic unit for detailed investigations. If, however, on initial screening the plasma methionine is between 0·2 and 0·6 mmol/l the test is repeated after one month. If the repeat test shows a normal pattern no further action is taken, but a persistent abnormality is investigated.

Of 12 babies identified because initial levels of plasma methionine were >0·6 mmol/l, homocystinuria was confirmed in 5 of them, one had galactosaemia with liver damage, one had α-1-antitrypsin deficiency with liver involvement, and one was found to have bacterial hepatitis after septicaemia. In the other 4 babies in whom raised methionine was associated with raised plasma tyrosine we were able to establish the diagnosis of hereditary tyrosinaemia.

I share the view that some infants with homocystinuria will not be identified by any neonatal screening method designed to detect raised plasma methionine. One baby with homocystinuria, a younger sibling of a known case, did not have a raised level of plasma methionine when tested on the 10th and 17th days after birth, but the level of homocystine in the blood was increased when measured on day 17.

We too have noticed a steady fall in the incidence of transient hypermethioninaemia since 1973 and have seen this trend reflected in the incidence of the other aminoacidaemias. This is shown in the Table. I agree that this decline is probably related to the wider use of low-protein milk formulae but would suggest that the occurrence of some transient aminoacidaemias may be due to temporary immaturity of enzymes necessary in the metabolism of relevant amino-acids.

Table *Incidence of transient aminoacidaemias per 100 000 infants screened (1972–78)*

Amino-acids	*1972*	*1973*	*1974*	*1975*	*1976*	*1977*	*1978*
Methionine	218	222	136	155	99	87	58
Phenylalanine (not exceeding 0·3 mmol/l)	232	76	90	122	78	40	48
Tyrosine	777	*	*	580	302	77	88
Generalised increase of amino-acids	414	281	247	214	175	129	144
Miscellaneous (basic amino-acids, glycine, etc.)	*	300	298	221	148	151	70

*Complete data not available.

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Lymphocyte response after surgery in the neonate

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SUMMARY Fourteen neonates born with congenital malformations were investigated for lymphocyte function before and after surgery. Total leucocyte and absolute lymphocyte counts were unaltered after surgery. The mean percentage of T-lymphocytes observed either pre- or postoperatively was considerably lower than that reported in older children and adults. While there was an increase in the percentage of B-lymphocytes after operation in the infants, the absolute number of B-cells remained unchanged. The preoperative transformation response of lymphocytes to PHA (mean $12 \cdot 9 \pm 5 \cdot 4 \times 10^3$ counts/min) was little different from the postoperative values (mean $12 \cdot 4 \pm 4 \cdot 4 \times 10^3$ counts/min). These results suggest that the neonate is immunologically different from older children and adults in its response to anaesthesia and surgery.

It is now widely accepted that anaesthesia and surgical trauma in children and adults results in immunosuppression (Donovan and Soothill, 1973; Cullen and van Belle, 1975). This immunosuppressive effect is apparent within 10–15 min of induction of anaesthesia (Espanol *et al.*, 1974) , is greatest in the immediate postoperative period (Park *et al.*, 1971; Slade *et al.*, 1975), and persists for 7 to 10 days (Jubert *et al.*, 1973). There is evidence that anaesthetic drugs depress both specific and nonspecific defences against infection and that this depression influences postoperative morbidity (Moudgil and Wade, 1976).

The lymphatic tissue of the neonate is mature for both cell-mediated and humoral immune response (Miller, 1977). The capacity to mount cellular and humoral immune reactions develops at between 9 and 15 weeks of gestation, but antigenic stimulation is necessary for antibody production on a large scale (Prindull, 1974). The immune system in the newborn in response to a sudden change of environment after birth has not been extensively studied and there are no data on the effect of anaesthesia and surgery on the immune response of the neonate. The purpose of this study was to determine whether an operation performed under general anaesthesia causes changes in the lymphocyte response of the neonate and, if so, to establish the quality of these changes.

Material and methods

Fourteen infants, 10 boys and 4 girls, born with congenital malformations were studied. Eleven were born at term, two at 38 weeks' gestation, and one at 36 weeks. Pregnancy was complicated by hydramnios in 3 cases. Delivery was normal in 12 babies, breech in one, and forceps-assisted in one. Average birthweight was 3·2 kg, with a range of 2·5 to 4·7. The various congenital anomalies in the 14 neonates were neural tube defects in 7, oesophageal atresias with tracheo-oesophageal fistulas in 3, small bowel atresias in 2, and anorectal anomalies in 2.

Samples of venous blood for various immunological parameters were obtained 2 hours before surgery, usually at the time when the blood sample for crossmatch was being taken, and again 18 hours after the operation. The average age of the infant at the time of the preoperative blood sample was 1·8 days.

The patients were premedicated with atropine 0·02 mg/kg 30 min before operation. Anaesthesia was induced with oxygen, nitrous oxide and 2% halothane, and relaxed for intubation with succinylcholine, 1 mg/kg. For the maintenance of anaesthesia, 50% nitrous oxide in oxygen and, if necessary, 2% halothane were used. Pancuronium bromide (Pavulon) 0·1 mg/kg was used for further

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relaxation in patients undergoing surgery for intestinal obstructions and oesophageal atresias.

The average operating time including anaesthesia was 95 min, with a range of 50 min to 3½ hours. Only one of the 14 infants required blood transfusion during surgery. Two babies were on antibiotics before blood samples were taken.

Blood samples for lymphocyte population studies and mitogen response to PHA were collected in sterile tubes containing preservative-free heparin (20 IU/ml). Blood for total leucocyte and absolute lymphocyte counts was collected in sodium EDTA blood tubes.

Total leucocyte and absolute lymphocyte counts. The leucocyte count was made on an electronic cell counter (Coulter Counter Model ZF), and the differential white cell counts were made on blood smears using Giesma stain. 200 leucocytes were counted to determine absolute cell numbers.

Separation of mononuclear cells. 2 ml heparinised blood was allowed to sediment at room temperature for an hour. The leucocyte-rich supernatant was layered on to a Ficoll-Hypaque gradient of density 1·077 (24 vol 9% Ficoll and 10 vol 33·9% Hypaque) and lymphocytes were separated after centrifugation at 800 *g* for 10 min. The lymphocytes were washed twice in medium 199 and adjusted to a concentration of 10^6 cells/ml in the same medium. This cell suspension was used for T-cell, B-cell, and null cell counts.

Spontaneous erythrocyte rosettes. 0·25 ml of cell suspension was mixed with an equal volume of a 0·5% suspension of washed sheep red blood cells (SRBC) and incubated at 37°C for 15 min. The cell preparations were then centrifuged at 200 *g* for 5 min at room temperature followed by incubation at 4°C for 18 hours. The cells were resuspended and counted in a Fuchs-Rosenthal haemocytometer. A minimum of 200 lymphocytes were counted and all lymphocytes binding 4 or more SRBC were accepted as positive.

B-lymphocyte identification. 0·1 ml of a working dilution of fluorescein-conjugated antiserum to whole immunoglobulin was added to an equal volume of cell suspension and incubated at 18°C for 30 min. The cells were then washed twice in medium 199, resuspended in one drop of phosphate buffered glycerol, and mounted on conventional microscope slides immediately before ultraviolet microscopical examination, using incident (epi) illumination.

PHA response. Cells collected in Ficoll-Hypaque gradient were resuspended in Dulbeccos Mod. medium (25 mmol/l Hepes buffer with L-glutamine) containing 10% fetal calf serum and 100 units penicillin and streptomycin/ml. Cultures were set up in triplicate in Steralin microplates, containing 10^5 cells in 200 ml medium and incubated for 3 days in 5% CO_2 and 95% air at 37°C.

PHA-P (Difco) was used as mitogen in doubling dilutions from 1/2 to 16×16^{-3}. After 68 hours' incubation, 0·4 μCi ^{3}H-thymidine was added to each culture and the cells were harvested on to glass fibre discs after a further 4 hours' incubation. The discs were washed twice in 10% TCA and twice in methanol, and then dried and counted in a liquid scintillation counter. A dose response curve to PHA was obtained for each infant.

Statistical method. The significance of difference between the mean preoperative and postoperative values was calculated using Student's *t* test for two independent observations.

Results

Total leucocyte and absolute lymphocyte counts. The total leucocyte count (Table 1) showed a wide variation in the numbers of leucocytes both pre- and postoperatively. Even though the mean total leucocyte count showed a drop from 17 264 cells/mm³ ($17\cdot3\times10^9$/l) preoperatively to 15 407 cells/mm³ ($15\cdot4\times10^9$/l) postoperatively, half of the patients showed an actual increase in the postoperative total leucocyte count. The preoperative absolute lymphocyte counts were not significantly different from postoperative counts (Table 1).

T- and B-lymphocytes. The percentage of B-lymphocytes increased after surgery in 9 out of 10 infants. While there was an increase in the mean percentage of B-lymphocytes after surgery, the absolute number of B-cells remained unaltered (Table 2). Both the

Table 1 *Total leucocyte and absolute lymphocyte counts in neonates pre- and postoperatively*

	No. tested	*Range*	*Mean ± 1 SD*
Total leucocytes/mm³			
Preoperative	14	8700 – 29 800	17 264 ± 6075
Postoperative	14	10 600 – 22 700	15 407 ± 3328 NS
Absolute lymphocytes/mm³			
Preoperative	14	2262 – 12 336	5350 ± 2953
Postoperative	14	2100 – 7293	4416 ± 1572 NS

NS = Not significant ($P>0\cdot05$).
Conversion: traditional units to SI—lymphocytes: 1000/mm³ ≈ 1·0 × 10⁹/l.

Table 2 *E-binding (T), SmIg-positive (B) lymphocytes, and null cells in neonates pre- and postoperatively*

	No. tested	*Percentage*		*Absolute no.*	
		Range	*Mean ± 1 SD*	*Range*	*Mean ± 1 SD*
E-binding lymphocytes (T-cells)					
Preoperative	10	6–65	38·4 ± 17·3	283–6168	2277 ± 1659
Postoperative	10	16–58	36·1 ± 12·4 NS	474–4230	1725 ± 1207 NS
SmIg-positive lymphocytes (B-cells)					
Preoperative	10	12–31	22·1 ± 6·7	282–2450	1286 ± 651
Postoperative	10	11–49	29·2 ± 10·7 NS	454–1969	1240 ± 556 NS
Null cells					
Preoperative	10	4–66	39·6 ± 18·6	108–6236	2448 ± 1689
Postoperative	10	15–56	34·7 ± 13·6 NS	504–2724	1446 ± 665 NS

NS = Not significant (P>0·05).
For conversion see Table 1.

percentage and the absolute number of spontaneous E-rosettes (T-cells) were unaffected by anaesthesia and surgery. The percentage of null cells was noticeably high in the infants and was not appreciably changed after surgery. The mean percentage of null cells was 39·6 ± 18·6 preoperatively and 34·7 ± 13·6 postoperatively (Table 2).

Table 3 *Maximum PHA mitogen response (counts/min × 10^3) in the neonate pre- and postoperatively*

	No. tested	*Mean + 1 SD*
Preoperative	9	12·9 ± 5·4
Postoperative	9	12·4 ± 4·4 NS

NS = Not significant (P>0·05).

PHA response. The rate of ^{3}H-thymidine incorporation after PHA stimulation was greatest at a concentration of either 0·06 or 0·1 μl/ml in all infants. The transformation response of lymphocytes to PHA did not change after surgery, the preoperative mean being 12·9 ± 5·4 × 10^3 counts/min and the postoperative being 12·4 ± 4·4 × 10^3 counts/min (Table 3). There was no significant difference at any of the PHA concentrations used in the dose response curve before or after surgery (Figure). Appreciable levels of spontaneous ^{3}H-thymidine incorporation (1·2 ± 0·9 × 10^3 counts/min) were observed in all patients. At optimum PHA concentrations, a wide variation of maximum incorporation of ^{3}H-thymidine was observed, especially in patients before operation.

Discussion

While most authors have reported that anaesthesia and surgical trauma in adults and older children produces depression of the cellular immune response

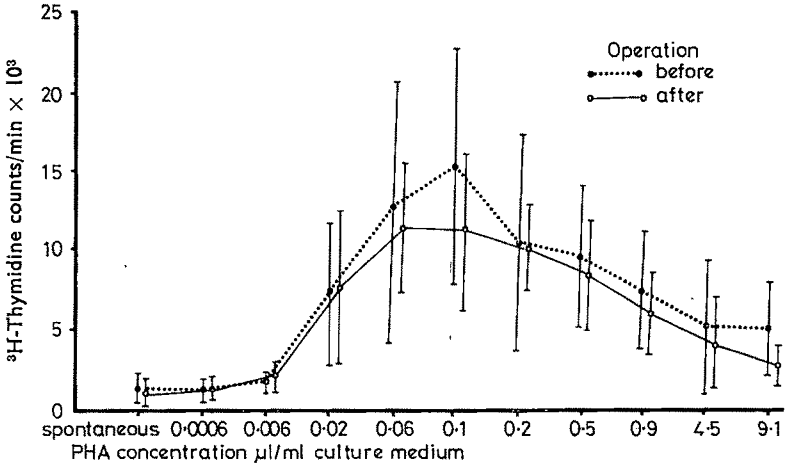

Figure *PHA response to increasing mitogen concentrations before and after surgery. Each point represents mean ± 1 SD for 9 patients.*

(Donovan and Soothill, 1973; Cullen and van Belle, 1975), we have been unable to support this finding in the neonate. No overall differences could be demonstrated between the preoperative and postoperative immune response. A number of factors must be considered in relation to this study in the neonate which may explain the differences in our results from those previously reported, and also may help to explain the clearly divergent reported observations on the effect of surgery on the immune response in adults.

When making comparisons of results in relation to the immune status of patients it is essential to select and control as closely as possible a homogeneous group of subjects and to eliminate wide variations in relation to age, degree of immunological sensitisation, clinical status, as well as factors that are known directly to affect immunological competence—such as therapeutic regimens, blood transfusion, and infection.

Age of the patient is of prime importance in relation to immune status, as T-lymphocyte subpopulations and mitogen responsiveness are diminished with increasing age (Augener *et al.*, 1974; Pisciotta *et al.*, 1967). Some patients in our study were relatively homogeneous in regard to age, with a mean age of 1·8 days and a range of 1 to 3.

All patients had a similar brief exposure to their antigenic environment since they were all directly transferred soon after birth from the maternity hospital to the referral centre for urgent surgery.

Several investigators have reported that immunosuppression after surgery is related primarily to the extent of tissue trauma, a more profound decrease in lymphocyte responses occurring after major rather than minor operations (Berenbaum *et al.*, 1973; Salo, 1978). The present study shows that major surgery in the neonate for congenital anomalies is not associated with depression in the immune responsiveness.

Total leucocyte and absolute lymphocyte counts were not significantly altered after surgery. This may be explained by the observations that the infant is undergoing active bone marrow generation with rapid alteration in peripheral blood leucocyte counts, coupled with a developing lymphocytosis relative to later life (Andersen and Andersen, 1974). This normally occurring lymphocytosis in the first few days of life may counteract any specific leucopenic effect of surgery in the neonate.

Similar conditions may explain the unaltered absolute numbers of T- and B-lymphocytes postoperatively. Even though 9 out of 10 infants showed an increase in the percentage of B-lymphocytes after surgery, this increase was not apparent in the absolute numbers owing to the wide range of total leucocyte counts present in the newborn. The mean percentage of T-cells observed in this study either pre- or postoperatively was considerably lower than that reported for older children and adults (Fleisher *et al.*, 1975). Similarly the percentage and actual numbers of null cells in the infant were higher when compared with the reported levels in adults.

These observations are further supported by our findings on mitogen response to PHA after anaesthesia and surgery. No significant change was found in the transformation response of lymphocytes to PHA after operation. However, an appreciable level of spontaneous ^{3}H-thymidine incorporation was observed in all patients ($1 \cdot 2 \pm 0 \cdot 9 \times 10^3$ counts/min). This may further reflect an active development of lymphocyte production and maturation taking place in the neonate.

These finding suggest that the neonate is immunologically different from older children and adults in its response to known immunosuppressive factors, such as anaesthesia and surgery. Further studies are required on factors that affect the immunological capacity of the neonate in order to understand more fully the complex immunological status of the developing infant in the first few days of life.

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Critical assessment of small bowel biopsy in children

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SUMMARY 176 biopsies of small bowel mucosa taken during a 5-year period from 162 children were reviewed, and 92 of them were subjected to quantitative measurement using surface/volume ratio and intraepithelial lymphocyte counting. There was good general agreement between stereomicroscopical appearance of fresh tissue, routine pathology reporting, and our independent histological assessment. Most of those in which there was divergence of opinion (11–15%) had intermediate mucosal changes. There was a significant difference between the surface/volume ratio for each of the three grades of histology ($P<0\cdot001$, $<0\cdot001$, $<0\cdot01$), indicating a relationship between qualitative and quantitative methods of assessment. The range of measurements in intermediate biopsies overlapped those of the other two grades. In the 92 biopsies there was a correlation between surface/volume ratio and intraepithelial lymphocyte count ($r = -0\cdot56$; $P<0\cdot001$) which may reflect our clinical experience, in that 88% of the biopsies were graded as either normal or flat (probable coeliac disease). Very short children had shorter villi than those with nonspecific diarrhoea and a more normal height.

Small bowel biopsy is the key investigation for the diagnosis of enteropathies, such as coeliac disease, and it is imperative that a proper interpretation of the intestinal histology is made. This is usually assessed subjectively and may be made more difficult by poor orientation of the mucosa before histological sectioning. In reviewing our experience we collated the histological material from all children biopsied between January 1972 and December 1977 inclusive. More than half of the specimens had also been subjected to morphological assessment using the techniques of surface/volume ratio measurement (Dunnill and Whitehead, 1972) and intraepithelial lymphocyte counting (Ferguson and Murray, 1971).

Methods

Patients. 162 patients (aged 3 months to 14·5 years) had biopsies of the small bowel mucosa because of clinical or laboratory features suggesting small gut enteropathy. A diagnosis of coeliac disease was made in 49 children. 11 others had possible postinfectious diarrhoea, 4 dermatitis herpetiformis, 4 giardiasis, 3 cystic fibrosis without associated bowel pathology, 2 an immunological disorder, 2 short bowel syndrome, and one each with isolated growth hormone deficiency, severe iron deficiency anaemia, and diabetes mellitus with pronounced hepatomegaly (Mauriac's syndrome). The biopsy was normal in 84 children.

Qualitative assessment. Peroral jejunal biopsies were taken under fluoroscopic control, at the ligament of Treitz with a Crosby-Kugler, one-hole, paediatric capsule. The specimen was placed on black filter paper, covered with normal saline, its mucosal surface immediately examined with a Wild stereomicroscope, the majority by one observer (J.F.T.G.), and graded as normal, intermediate, or flat according to the classification of Shmerling (1970). The tissue was then fixed in 10% formalin and processed for routine histological reporting by a pathologist. The same slides were graded independently (J.F.T.G.) as normal, intermediate, or flat before the pathology report was known. It is these two forms of histology which are referred to subsequently, but it is with the independent grading that quantitative measurements are compared.

Quantitative measurements. These were made without reference to the above findings in 92 biopsies.

Surface/volume ratio (SVR)

This was measured (Dunhill and Whitehead, 1972) by viewing the histological specimen through a

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graticule inserted in the microscope eyepiece. Inscribed on the graticule were (15 lines of equal length connecting the vertices of a regular hexagonal point network (Weibel, 1963). SVR is given by the formula c:lh, where c is the total number of times a line *cuts* the epithelial surface, h the total number of times the end points of a line *hit* the mucosa between muscularis mucosae and epithelium. At least 200 hits were made. The mucosal volume (MV) is the mean number of hits h, for each position of the graticule in relation to the mucosa. The length of the line, l, projected on the histology was 1·4 mm. Magnification was kept constant throughout.

Counts of intraepithelial lymphocyte (IEL)
These were made according to Ferguson and Murray (1971). Differential counts of cell nuclei were carried out within the epithelium where the plane of section passed vertically through basement membrane and enterocytes. Their nuclei and those of lymphocytes could thus readily be distinguished; goblet cells were ignored. In histologically normal and intermediate specimens, counts were made on the sides and tips of the villi and in flat biopsies surface cells were counted. In most biopsies at least 400 epithelial cells were counted. In a few flat biopsies however, which were small in size with distortion of the epithelial cells, only 200 could be accurately counted. The results were expressed as IEL per 100 epithelial cells.

Normal ranges were derived by plotting cumulative percentages on probability graph paper (Hoffmann, 1963). Statistical comparisons were made using the SPSS system (Nie *et al.*, 1975) and Student's *t* test.

Results

Qualitative assessment. By comparison with our independent grading, stereomicroscopical examination graded the majority of normal and flat biopsies correctly (Table 1). This was not so for intermediate changes, as there was a tendency for stereomicroscopy to suggest a degree of abnormality less severe than could be confirmed histologically by us.

Table 1 *Independent histological grade compared with stereomicroscopic grade*

Independent grade	*Stereomicroscopic grade*				
	Normal	*Intermediate*	*Flat*	*NE*	*Total*
Normal	95	8	—	5	108
Intermediate	8	11	2	—	21
Flat	—	8	37	2	47

NE = Not examined.

Table 2 *Independent histological grade compared with pathology report*

Independent grade	*Pathology report*			
	Normal	*Intermediate*	*Flat*	*Total*
Normal	93	12*	—	105
Intermediate	—	19	—	19
Flat	—	4*	44	48

*See Table 5.

Comparison of the pathology report with our independent grade tended also to be in general agreement (Table 2). Of the 35 biopsies reported as intermediate however, independent grading was in agreement in 19 and, of the remaining 16, 12 were normal and 4 flat; these 16 are discussed below.

Quantitative measurements. The SVR between each of our three independent grades showed highly significant differences (Tables 3 and 4). There was no overlap between the range in normal and flat mucosae, but the SVR of the intermediate grade overlapped each of the others to a considerable degree. Significant differences were also present in MV between normal and flat biopsies. There was no difference between the intermediate and either of the other two grades. Each of the ranges for MV greatly overlapped.

The normal range for lymphocytes per 100 epithelial cells (probability graph plot) was 3–37. IEL counts were significantly different when flat biopsies were compared with other grades. The range in all however, overlapped considerably. There was a significant correlation between the IEL count and SVR ($r = -0·56$; $P<0·001$), although this was not the case within the normal or flat grades ($r = -0·03$).

Table 2 shows 19 biopsies about which the pathology report and independent grading were in agreement. There was a difference of opinion about the other 16 specimens (already mentioned). These were coded and submitted to 'blind' quantitative analysis. Data for SVR, MV, and IEL were within the ranges quoted in Table 3, but only SVR and MV provided clear separation between normal and flat grades (Table 5).

We studied 13 biopsies in which the muscosa was graded as either normal or intermediate. These were taken from 10 children with coeliac disease who were taking a gluten-free diet or undergoing gluten challenge (Figure). In 11 the SVR and MV divided those with qualitatively normal mucosa from those with intermediate changes; 2 were not assessed for technical reasons. None with a SVR below a value of 40 or MV above 11 had normal morphology. Gluten challenge tended to reduce the SVR and

Table 3 *Independent histological grading in relation to the quantitative data*

Independent grade	*n*	*SVR*		*MV*		*IEL*	
		Range	*M ± SD*	*Range*	*M ± SD*	*Range*	*M ± SD*
Normal range (probability curve)		26–64		8·6–12·7		3–37	
Normal	44	30–68	45 ± 10	8·3–13·2	10·9 ± 1·2	4–58	23 ± 12
Intermediate	12	6–60	27 ± 15	8·4–13·3	11·1 ± 1·8	9–54	32 ± 15
Flat	36	5–29	15 ± 6	8·8–26·4	12·2 ± 2·7	28–92	49 ± 14

Table 4 *Statistical comparison (P values) of data in Table 3*

Grades compared	*SVR*	*MV*	*IEL*
Normal with flat	<0·001	<0·02	<0·001
Normal with intermediate	<0·001	>0·05 NS	>0·05 NS
Flat with intermediate	<0·01	>0·05 NS	<0·002

Table 5 16 *biopsies graded intermediate in pathology report*

Independent histological grade	*n*	*SVR (M±SD)*	*MV (M±SD)*	*IEL (M±SD)*
Normal	12	38±5 (31–47)	10·4±1·0 (9–12)	25±10 (13–58)
Flat	4	12±1 (11–14)	13·8±1·6 (13–17)	40±4 (34–44)
P		<0·001	<0·001	<0·001

Range in parentheses.

Table 6 *Analysis of quantitative data by presenting complaint in those with normal biopsy*

Presentation	*n*	*SVR (M±SD)*	*MV (M±SD)*	*IEL (M±SD)*
Diarrhoea	12	49±9	10·3±1·3	22±15
Short stature only	18	40±13	11·0±1·2	20±9
P		<0·05	NS	NS

increase the MV, while a gluten-free diet reversed these trends. One child who was being gluten challenged had a normal mucosa, but this had been in progress for only one week. One other had intermediate changes although a normal IEL count, which may have been because the biopsy was from the second part of the duodenum. The IEL counts did not always correspond to morphological grading. High counts were noted in 4 children with intermediate changes who were taking a normal diet. Two other patients had normal IEL counts, but in each, challenge with gluten powder, 5 g daily, had begun only one week before; when biopsied again having been on a normal diet for some months each had abnormally high counts (Figure).

Four patients with giardiasis, all of whom had normal mucosae, had widely differing IEL counts; 3 were within the normal range, but one child with hypogammaglobulinaemia and a heavy infestation had a count of 58. Three children with dermatitis herpetiformis and normal mucosae had normal IEL counts (18, 22, 25) and one, graded as flat, a count of 55.

Finally, quantitative data in children presenting with short stature (height <3rd centile) in whom no intestinal lesion was found, had a significantly smaller mean SVR than those whose complaint was of non-specific diarrhoea (Table 6). The MV and IEL counts in the two groups however, were virtually identical.

Discussion

Jejunal biopsy, now accepted as the key investigation in the diagnosis of small bowel enteropathy, has shown that the range of possible changes in

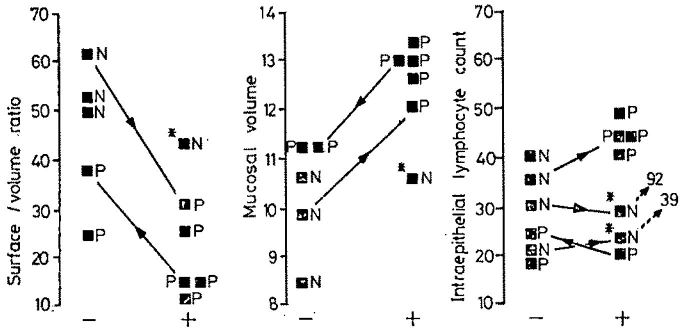

Figure *Quantitative measurements in children with coeliac disease in whom biopsies were not flat because the children were on a gluten-free diet (—) or being gluten challenged (+); N, normal mucosa; P, intermediate changes. Arrows indicate serial biopsies in 4 children. Asterisk indicates data on two patients on gluten challenge for one week only.*

various disorders is very wide. As these changes are usually described in purely subjective terms it is not surprising that interobserver variation occurs (15% in this study) or that this is more likely in the intermediate part of the range, rather than at either extreme (Table 2). Similar variation was experienced when stereomicroscopical examination of fresh tissue was compared with our independent histological grading (Table 1). Although these two methods of examination are not strictly comparable, differences (11%) again tended to be in the intermediate group. Others have reported similar findings (Rubin and Dobbins, 1965; Anderson, 1966). Two further problems which lead to interpretational difficulty are variations in villous architecture found between duodenal and jejunal mucosa (Anderson, 1966), and perhaps more important, technical problems in orientating the specimen before histological sectioning (Brandborg *et al.*, 1959). This is more likely if the biopsy is very small as may be the case if a paediatric instrument is used.

One attempts to combat such inherent variability by taking specimens from a constant site in the gut (Rubin and Dobbins, 1965), striving for perfection in preparing the mucosa so that villi are sectioned vertically, rather than tangentially, and by examining them oneself. It is also helpful to carry out quantitative assessment on biopsies where histological reports are equivocal (Table 5) and, although not the case throughout much of the current study, it should be helpful to have the same pathologist report on all biopsies. Standardisation and comparability are more important with the increasing use of serial biopsies in children with suspected coeliac disease.

Various quantitative assessment methods have been used in the past. Risdon and Keeling (1974) pointed out, that to be of value an assessment must be accurate, reproducible, and have well-defined normal ranges. More arbitrary methods—such as the measurement of villus length and width—fail to satisfy these criteria (Madanagopalan *et al.*, 1965). The methods used here have been validated (Ferguson and Murray, 1971; Risdon and Keeling, 1974) and the normal ranges seem reproducible, although they will not overcome difficulties imposed by specimen distortion or poor histological preparation. Counting of IEL might more accurately be done per unit length of mucosa (Skinner and Whitehead, 1976), but provided the original method is followed, intercentre variation should be negligible.

A highly significant difference in SVR was found between the three histological grades, thus indicating a close relationship between quantitative and qualititative assessments. The fact that the range for normal mucosa overlapped that for intermediate changes accords with the findings of Risdon and Keeling (1974) and tends to reduce the clinical value of SVR in distinguishing biopsies with mild changes from normal (Table 3). On the other hand, when used to assess serial biopsies from the same individual SVR may be more helpful (Figure).

We confirmed that flat mucosa had a volume significantly greater than normal, which is related to crypt hyperplasia, mucosal swelling, and oedema (Whitehead, 1971). The actual values recorded for MV in each of the three grades were uniformly lower than those of others (Dunnill and Whitehead, 1972; Risdon and Keeling, 1974). Since MV is an absolute measurement ($\bar{h}$), as opposed to a ratio, one might expect a greater intercentre variation than with SVR. These differences could be related to such things as different degrees of handling mucosae after biopsy, or to technical factors—for example varying degrees of tissue shrinkage during preparation. Because of these factors and the fact that ranges of the three grades of mucosa overlap, MV is considered less useful than SVR, particularly in comparing data between different centres, unless identical methods are strictly followed.

Unlike data for SVR and MV in normal biopsies, those for IEL counting showed a distribution which was mildly skewed towards the upper end. This was probably because we had as our group of normal biopsies, tissue which, although architecturally normal, was taken from children, some of whom had bowel symptoms or growth failure, rather than from truly normal individuals, such as the normal siblings of coeliac patients (McNicholl *et al.*, 1976; Mavromichalis *et al.*, 1976). None the less, by using the probability plot as a means of eliminating values at the extremes of the range which are less likely to be completely normal, in spite of their villous architecture, we derived a normal range (and mean) similar to those quoted (Ferguson, 1977).

We have found a significant relationship between morphological alteration in the mucosa and lymphocytic infiltration of the epithelial layer. This in no way implies a causal link between the two and in clinical practice a number of our cases demonstrated that the two modalities of abnormality behaved in an independent manner. A child of 20 months with a fatal defect of cell-mediated immunity, who had intermediate changes, with SVR of 5·7, had an IEL count of only 9. Several of our flat biopsies characteristic of coeliac disease have also had low IEL counts, which may reflect conscious or unconscious withdrawal of gluten from the diet in children old enough to select their own food. On the other hand, 3 young children had morphologically normal biopsies but abnormally high IEL counts. The most striking was a child with immunodeficiency and heavy giardiasis whose IEL count was 58. The other two children with diarrhoea and failure to thrive also had counts >40 and were clinically similar to the infants reported by Ferguson *et al.* (1976). It was thought their high IEL counts may have been an indication of food allergy. Whether this was the case in our patients we cannot be certain, however, it may be significant that in the group of children presenting with nonspecific diarrhoea, the IEL counts were similar to those with short stature *per se* (Table 6). None the less, a correlation has been shown between SVR and IEL counts and it seems likely that this is because 88% of our biopsies proved to be either flat, the majority with high counts consistent with coeliac disease, or normal, most having normal IEL counts. Others who have a quite different practice, with many more biopsies of intermediate grade have recently reported no relationship between surface area (c), one of the two variables in the SVR, and the IEL count (de Peyer *et al.*, 1978).

One area where quantitative methods of assessment may prove to be particularly useful is in following serial biopsies from the same patient. So far we have had only a limited experience of this. McNicholl *et al.* (1976) studied 36 children, using IEL counting, over a number of years and feel that quantitative assessment is better than subjective methods of interpretation.

Very short normal children, the majority with genetic short stature, had villi with significantly smaller surface areas than those presenting with nonspecific diarrhoea (Table 6) and it would seem likely that this is because their villi are actually shorter. This seems a possible explanation since the mucosal volumes, the one other variable, was not significantly different in the two groups. Indeed it seems reasonable that very short children may have proportionately shorter villi.

The time required to carry out these counting techniques is brief. The SVR and MV can with practice be done in 2–3 minutes and the IEL count in a comparable time.

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Use of growth hormone-gel

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SUMMARY We evaluated the efficacy of a depot preparation of growth hormone (GH) in a 15% gelatin solution (GH-gel) in the treatment of 15 growth hormone-deficient children. The studies were designed to see if prolonging absorption of GH to achieve lower more physiological concentrations of GH in plasma would decrease the frequency of injection, reduce the amount of GH needed for effective therapeutic response, and improve the response to long-term treatment. We found that after a single dose of GH-gel the plasma concentrations of GH were lower than those achieved after the standard aqueous preparation. The preparation was efficacious in promoting growth and our 1st study of 6 patients suggested that GH-gel given twice a week had a growth response equal to that of the three-times a week aqueous schedule. However both schedules resulted in the frequently observed decreased growth rate during the second treatment year. Our 2nd study, attempting to ameliorate this waning effect by using the GH-gel preparation twice a week in a weight-adjusted dose during the entire second year did not resolve the problem. Thus, GH in depot gel results in more physiological plasma concentrations of GH and may be beneficial in reducing the quantity of hormone needed and the injection frequency but it does not offer a solution to the waning response to the long-term administration of GH.

The administration of growth hormone (GH) extracted from pituitaries has provided successful treatment for children with growth hormone deficiency. However, the optimal dose and administration schedule has yet to be established (Preece *et al.*, 1976; Frasier *et al.*, 1977). The quantity of GH given to each child is limited by its availability and cost, and the need to give the preparation repeatedly by the intramuscular (IM) route.

The usual method of administration results in an unphysiological pattern of the concentration of GH in plasma. After a single IM injection of GH in aqueous solution, peak concentrations are reached in 2–4 hours. The peak levels of GH are in the range usually found in patients with acromegaly. After this very high peak there is a rapid decline in the concentration of GH and the hormone disappears from plasma within 12–24 hours (Frasier *et al.*, 1969).

We thought that a depot preparation of GH might prolong absorption from the site of injection and maintain lower but more physiological plasma concentrations for longer periods of time, thus decreasing the amount of GH needed to maintain an effective therapeutic response, and improving the therapeutic response to long-term GH administration. Our experience with GH in a 15% gelatin solution (GH-gel) in the treatment of 15 patients with growth hormone deficiency is reported.

Materials and methods

Patient population. Patients with growth hormone deficiency diagnosed by testing as previously described (Lippe *et al.*, 1971) and followed up at the UCLA Pediatric Endocrine Clinic were studied under an approved National Pituitary Agency (NPA) protocol. The patients ranged in age from 7–15 years, were all prepubertal at the time of starting GH treatment, and were all growing at a rate of 3 cm or less in the year before treatment.

Preparation of GH for injection. Aqueous growth hormone was prepared by adding sterile, distilled water to GH as provided by the NPA. Gelatin (gel) USP was prepared as a 15% weight/volume solution

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in freshly distilled water and packed in 10 ml rubber-stoppered vials without preservative. The vials of gelatin were sterilised by autoclaving. To prepare GH for injection, the gelatin vial was warmed to liquidity under warm, running water by the patients' parents and used as diluent for the NPA GH in the same way that sterile water was used. Once mixed, each GH-gel vial provided material for 4–6 injections. The material was refrigerated between injections and rewarmed to liquidity before administration of each dose.

Laboratory methods. The concentration of GH in plasma was measured by a double antibody radioimmunoassay (Boden and Soldner, 1967). Binding antibodies to GH were measured as previously described (Frasier *et al.*, 1974).

GH blood levels. The concentrations of GH achieved in plasma, after a single IM injection of either 2 international units (IU) GH in aqueous solution (GH-AQ) or 2 IU GH-gel, were measured in 6 patients. All patients had an indwelling scalp vein needle with a heparin lock placed in a hand vein and blood was sampled at 0, 1, 2, 4, 6, 8, 12, 18, 24, and 30 hours after the injection. In those patients receiving GH-gel, sampling continued at 36, 42, 54, 60, and 72 hours. Plasma was separated and stored at −20°C until assay.

Treatment protocols.

Study 1

Six patients entered an initial 30-month crossover study to test the efficacy of the gel preparation and to examine the therapeutic response to a lower dose of hormone in the depot form. Cases 1–3 were started on 2 IU of GH three-times a week (6 IU/week) in aqueous solution (GH-AQ) for 6 months followed by 2 IU twice a week (4 IU/week) in gel for 6 months. After a 6-month period during which no GH was administered, these patients resumed treatment with 6 months of GH-gel (2 IU twice a week) followed by 6 months of GH-AQ (2 IU three-times a week). Cases 4–6 followed a reverse schedule. They received GH-gel for 6 months followed by GH-AQ for 6 months. After a 6-month period of the treatment they received GH-AQ followed by GH-gel.

Study 2

After the crossover study had been completed, a second group of 9 patients (Cases 7–15) began a 30-month regimen of GH therapy with doses adjusted for weight. Therapy was begun with GH-AQ in a dose of 0·1 IU/kg per injection, administered three-times a week (0·3 IU/kg per week). After one year of this schedule and a 6-month period of no treatment, GH-gel was administered at a dose of 0·15 IU/kg twice a week. Thus, patients received the same weekly dose as during the first year (0·3 IU/kg per week) in two injections. The dose of GH-gel was again adjusted to body weight at the beginning of the second year.

Results

GH blood levels. The mean plasma concentrations of GH reached after single injections of GH-AQ and GH-gel are shown in Table 1. The GH-AQ preparation resulted in a rapid increase in GH by one hour, a wide peak of 128·4 ± 77·5 mU/l at 2 hours, and concentrations in excess of those obtained after the gel preparation until 8 hours after the injection. By contrast, there was no clear peak after the gel preparation, and the concentrations achieved in the first 8 hours were much lower than with the aqueous, with maximum concentrations of only 37·9 ± 8·8 mU/l. By between 12 and 18 hours the gel preparation had maintained levels in excess of the aqueous preparation and by 24 hours both resulted in virtually undetectable concentrations. When we looked at the peak concentrations of GH achieved by each patient, irrespective of time, the patients receiving GH-AQ had a peak of 158·6 ± 62·2 mU/l (SEM) with a range of 95·7–283·1 mU/l, while the mean peak of those receiving GH-gel was 46·6 ± 11·9 mU/l and the range 26·7–68·0 mU/l.

While the number of patients in each group is small and the variability great (precluding meaningful statistical analysis), there are clear differences in the pattern and concentrations of GH achieved in blood after the two modes of administration. The levels and

Table 1 *Plasma growth hormone (GH) concentrations after single injections of GH-AQ and GH-gel*

Time (hours)	*Plasma GH (mU/l)**	
	GH-AQ (n=3)	*GH-gel (n=3)*
0	<4·0	<4·0
1	94·9 ± 66·9	8·5 ± 4·6
2	128·4 ± 77·5	22·1 ± 9·5
4	79·9 ± 12·1	37·1 ± 15·8
6	68·0 ± 13·9	37·4 ± 8·8
8	35·5 ± 3·1	32·5 ± 7·7
12	19·6 ± 5·6	29·6 ± 5·1
18	<4·0	17·5 ± 8·0
24	<4·0	<4·0
30	<4·0	<4·0
36	—	6·9 ± 3·7
42	—	<4·0
48	—	<4·0
54	—	<4·0
60	—	<4·0
72	—	<4·0

*Mean ± SEM.

Conversion: SI units to traditional units—1 mU/l = 0·6 ng/ml.

pattern after GH-AQ are similar to those which we previously reported (Frasier *et al.*, 1969). In contrast, the administration of GH-gel leads to a slower increase in blood levels, a lower and more prolonged peak in growth hormone concentration, and persistence of detectable growth hormone for a longer time.

Study 1

Table 2 shows the growth rates for Cases 1–6 while they received alternate courses of GH-AQ and GH-gel. The results of the first year of this study were confounded by the development of hypothyroidism in 3 patients (Lippe *et al.*, 1975). However, when the 6-month periods during which patients with untreated hypothyroidism are eliminated from consideration, it is clear that in the first year of treatment there was no overall difference in the rate of growth during the administration of GH-AQ (3·9 ± 0·2 cm/6 months) and during the administration of GH-gel (3·9 ± 0·3 cm/6 months). The small numbers preclude meaningful statistical comparison of the effects of the sequence in which each GH preparation was given.

In the second year of treatment there was also no difference in the rate of growth during the administration of GH-AQ (3·2 ± 0·2 cm/6 months) and the administration of GH-gel (3·1 ± 0·2 cm/6 months). The sequence in which the two GH preparations were given did not significantly alter the overall response. Patients who received GH-AQ first grew 6·2 ± 0·1 cm/year and patients who received GH-gel first grew 6·4 ± 0·2 cm/year.

However, there was a decrease in the rate of growth during the second year of GH administration. The growth rate for all treatment periods in which hypothyroidism was not a variable ($n = 9$) during the first year was 3·9 ± 0·2 cm/6 months. During the second year of treatment the growth rate for all treatment periods ($n = 12$) decreased to 3·1 ± 0·2 cm/6 months ($P<0{\cdot}01$).

Table 2 *Growth rate (cm/6 months) while receiving alternate courses of GH-AQ and GH-gel*

Case	*First year*		*Second year*	
	GH-AQ 1st 6 months	*GH-gel 2nd 6 months*	*GH-AQ 2nd 6 months*	*GH-gel 1st 6 months*
1	4·5	4·5	2·6	3·2
2	4·3	4·2	3·7	3·5
3	3·5	*	2·9	2·7
	2nd 6 months	*1st 6 months*	*1st 6 months*	*2nd 6 months*
4	3·7	*	2·9	3·6
5	*	3·7	4·0	2·1
6	3·3	3·3	3·2	3·2
Mean±SEM	3·9±0·2	3·9±0·3	3·2±0·2	3·1±0·2

*Hypothyroidism developed during these 6-month intervals.

Study 2

Table 3 shows the growth rates of Cases 7–15 during the year they received GH-AQ (0·1 IU/kg three-times a week) and during the year they received GH-gel (0·15 IU/kg twice a week). Growth rates for the 6-month 'off' period between the two treatment years have been extrapolated to a 12-month period and are shown for comparison. As hypothyroidism had been a problem in the 1st study, these patients were frequently monitored and in the one patient in whom the T4 decreased precipitously (Case 7) supplementary thyroxine was instituted within weeks.

The growth rate of 8·5 ± 0·4 cm/year during the first year of GH-AQ compares favourably with the therapeutic responses seen in other studies. In the second year with the weight-adjusted GH-gel preparation, there was a significant decrease ($P<0{\cdot}001$) in rate to 5·6 ± 0·4 cm/year.

Sera obtained from 7 patients after 6–12 months of GH-gel were tested for binding antibody to GH. Significant antibody was present in two samples.

Discussion

The most commonly used treatment regimens for the administration of GH to hypopituitary children are based on empiric observations of successful therapy (Raben, 1958; Escamilla *et al.*, 1961). Actual dose schedules, however, vary between countries and investigative protocols. Some schedules use doses which vary with body size or weight (Ferrandez *et al.*, 1970; Hall and Olin, 1972; Kirkland *et al.*, 1973; Frasier *et al.*, 1977), while others do not (Tanner *et al.*, 1971; Aceto *et al.*, 1974; Preece *et al.*, 1976). The variables of patient heterogeneity, additional hormonal requirements, and age at start of treatment have made the analysis of results difficult and have all contributed to less than ideal recommendations for the initial dose of GH. Administration of aqueous preparations results in radioimmunoassayable concentrations of GH which quickly reach very high

Table 3 *Growth rate (cm/year) while receiving GH-AQ followed by GH-gel*

	Cases									*Mean± SEM*
	7	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	
GH-AQ growth	7·8	9·4	7·6	7·7	7·0	8·4	10·7	8·5	9·0	8·5±0·4
No treatment	0·4	1·3	1·0	1·1	3·3	2·6	2·0	1·6	3·0	1·8±0·3
GH-gel growth	4·0	7·3	5·0	5·0	5·8	6·5	5·9	5·1	8·0*	5·6±0·4

*Entered puberty, rate not included in mean.
†$P<0{\cdot}001$, ‡$P<0{\cdot}001$ v. either treatment year.

levels and then fall rapidly. Long periods ensue before the next injection during which GH is undetectable (Frasier *et al.*, 1969). Thus, the present methods of administration result in abnormal patterns of plasma hormone levels characterised by peak concentrations, similar to those seen in acromegaly.

The current study was undertaken to test the efficacy of a depot GH-gelatin preparation designed to prolong time of absorption. We hoped to achieve adequate growth with less frequent injections and to reduce the total amount of hormone administered. We also studied the effect of GH-gel in ameliorating the deceleration in growth rate experienced by most patients after the initial rapid growth of the first year of treatment.

Our results demonstrate that the IM administration of a single injection of GH in gelatin reduces the peak concentration of GH and prolongs its absorption when compared with an injection of the same amount of GH in aqueous solution. The peak concentrations achieved after the injection of GH-gel resemble those seen in association with sleep in normal children (Underwood *et al.*, 1971; Eastman and Lazarus, 1973).

Although the number of observations was limited by the development of hypothyroidism in 3 patients, our initial study appears to indicate that GH-gel (2 IU twice a week) is as effective as an aqueous solution of GH (2 IU three-times a week) during both the first and second year of treatment. Thus, the administration of GH in gelatin appears to have stimulated the same rate of growth as aqueous GH with a significant saving in the quantity of hormone. Theoretically these savings would provide treatment for one more patient for every 2 currently being treated. At the same time, the number of injections and cost of treatment would be reduced. Because the number of patients treated in our study is small, these conclusions must be considered tentative. A larger group of patients needs to be treated with GH in gelatin to test the validity of our preliminary results.

As in previous studies in which GH was given for more than one year, the response waned during the second 12 months of GH therapy (Soyka *et al.*, 1970; Kirkland *et al.*, 1973; Aceto *et al.*, 1974; Frasier *et al.*, 1977). In our 2nd study we attempted to ameliorate this waning effect by administering GH-gel in the same total weekly dose as in the earlier GH-AQ therapy, using twice-weekly rather than three-weekly injections. We were not successful. The growth rate in patients receiving GH-gel was significantly less than that observed during the previous year of therapy with GH-AQ. In view of the comparable effects of the two GH preparations during the second year of our initial study, this diminished response is most likely due to time and not to the preparation. As previous analysis (Frasier *et al.*, 1977) indicates that a three-times a week dose schedule may be preferable to twice a week, we might have been more successful if GH-gel had been given three-times a week in a dose of 0·1 IU/kg. This hypothesis remains to be tested. A solution to the problem of waning response as observed in this and other studies remains to be found.

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Pulmonary hypoplasia: lung weight and radial alveolar count as criteria of diagnosis

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SUMMARY A working definition of pulmonary hypoplasia (PH) was established by retrospective assessment of lung growth both in recognised and hypothetical PH-associated conditions. Lung weight: body weight ratios (LW:BW) were calculated, and morphometry was determined by the radial alveolar count (RAC) (Emery and Mithal, 1960). Both parameters were reduced compared with those of normal controls in diaphragmatic hernia, anencephalus, anuric renal anomalies, chondrodystrophies, and osteogenesis inperfecta. Comparison of LW:BW ratio and RAC indicated that the RAC was the more reliable criterion of PH, LW:BW ratio of ≤0·012 (67% of mean normal ratio) and/or RAC of ≤4·1 (75% of mean normal count) are suggested as diagnostic criteria of PH. Evidence of PH was incidentally discovered in a number of clinically unsuspected cases and retrospectively clarified the clinical and radiological findings. Routine assessment of lung growth should be an essential part of the neonatal necropsy.

Pulmonary hypoplasia (PH) is a poorly defined condition considered to be almost invariably secondary to other anomalies and is usually diagnosed in association with them; primary or isolated PH has not been reported (Reale and Esterly, 1973). PH is lethal within hours of birth in many instances of diaphragmatic hernia (Potter, 1961; Kitagawa *et al.*, 1971; Reale and Esterly, 1973), anencephalus (Potter, 1961; Naeye and Blanc, 1971; Reale and Esterly, 1973), anuric renal anomalies with oligohydramnios (Potter, 1972; Reale and Esterly, 1973; Perlman and Levin, 1974; Thomas and Smith, 1974), and skeletal anomalies restricting thoracic volume (Finegold *et al.*, 1971). There is however a spectrum of severity of PH, often proportional to the severity of the underlying condition, and sublethal forms exist (Kohler and Babbitt, 1970; Chatrath *et al.*, 1971; Perlman *et al.*, 1975).

Because histological findings lack specificity (Potter, 1961; Reale and Esterly, 1973), diagnosis depends on detection of low lung weight in relation to body weight (low LW:BW ratio), or of low alveolar counts determined by morphometric methods (Reale and Esterly, 1973). Severe PH is easy to diagnose at necropsy from the low LW:BW ratio alone, but lesser or borderline PH is more difficult to establish. There has been only one study of both LW:BW ratio and morphometry in a substantial number of pathological cases (Reale and Esterly, 1973).

These diagnostic criteria of lung growth were studied in an attempt to establish a working definition of PH. Lungs of patients dying perinatally with PH-associated conditions were examined. In addition to these anomalies, neonates with other conditions in whom there were theoretical grounds to anticipate PH were examined.

Materials and methods

Material was obtained from the pathology departments of the Hadassah University Hospital, Jerusalem; Kaplan Hospital, Rehovot; and the Soroka Medical Centre, Beer-Sheva. About 200 liveborn and stillborn subjects were selected according to recognised PH associations (diaphragmatic hernia, anencephalus, anuric renal anomalies, chronic amniotic fluid leakage, and chondrodystrophies) and, in unprecedented cases, where PH was anticipated on theoretical grounds (osteogenesis imperfecta, hydrops fetalis). In addition, PH was identified incidentally in some patients who died during the study period because of a low LW:BW ratio at necropsy (central nervous system anomalies, gross ascites due to long-standing meconium peritonitis). No patient with PH lived for more than 72 hours.

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'Normal' control liveborn and stillborn infants were selected randomly, but subjects with birthweights outside the 10th to 90th centile for gestational age were excluded. Patients with clinically diagnosed and pathological confirmed lung disease—such as hyaline membrane disease and meconium pneumonitis—or with congenital anomalies including heart defects other than those with PH associations were also excluded. In all control infants death resulted from either perinatal asphyxia or traumatic intracranial haemorrhage within 3 days of birth.

The following information was obtained from the necropsy record: sex, gestational age, body weight, lung weight, age at death, anatomic diagnoses, and cause of death. LW:BW ratios were computed.

Morphometry was performed by one of us (S.A.A.) at microscopical magnification of × 40, using a modification of the method of Emery and Mithal (1960), without knowledge of the anatomical diagnoses or cause of death. Before beginning the study, experience of interobserver error was obtained with the help of Professor E. Rosenmann: the error was <± 10%. A line was dropped from the centre of each respiratory bronchiole (bronchioles only partially lined with epithelium) to the nearest connective tissue septum at right-angles to the epithelium. The number of alveolar septi (as distinct from the number of alveoli counted by Emery and Mithal) cut by this line were counted. At least 10 counts were made for each patient, mainly from 2–3 histological sections.

Mean values of LW:BW ratios and of RACs and SDs of the mean were calculated for each diagnostic group. The significance of the difference of the means of each of the pathological groups compared with the control group was determined by Student's *t* test. Subgroups of infants <36 weeks' gestation and >35 weeks' gestation were treated statistically in the same manner and compared.

Results

Of about 200 cases screened for study, 111 had adequate perinatal data and histological preparations suitable for morphometry. LW:BW ratios were not available in 12 cases. Mean gestational age and mean birthweight were similar in each group. The data for LW:BW ratio and RAC for infants of gestational ages <36 weeks were compared with data for >36 weeks and there was no significant difference, so the total data were analysed.

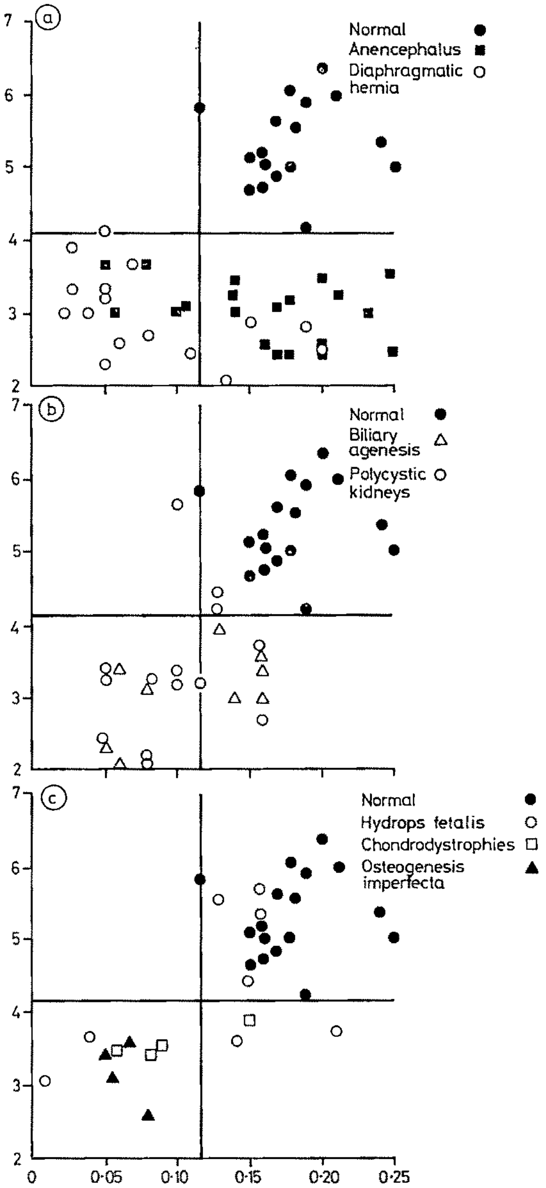

Figure *Comparison of lung weight:body weight ratio and radial alveolar count for each aetiological category as indicated. Values for individual patients are plotted according to absolute values of LW:BW ratio (abscissa, bottom), and mean RAC (ordinate, left). Additional horizontal and vertical lines, respectively, represent the values for the lower limits of normal for RAC and LW:BW ratio.*

With the exception of LW:BW ratios in anencephalics, LW:BW ratios and RAC were much reduced in each pathological group (Table). The results are illustrated graphically by plotting LW:BW ratios against RAC (Figure). Lines were drawn to indicate the lower limits of normal for each of the two parameters. The number of measurements below the normal range (mean −2 SDs) for each

Table *Lung weight; body weight ratios and radial alveolar counts in different aetiological categories*

Group	*Category*	*Mean gestational age (weeks)*	*Mean birthweight (kg)*	*Lung weight:body weight ratio*				*Radial alveolar count*			
				No. of cases	*Mean*	*SD*	*Range*	*No. of cases*	*Mean*	*SD*	*Range*
1	Normal	38	2·8	17	0·018	0·003	0·012–0·025	17	5·3	0·6	4·1–6·3
2	Diaphragmatic hernia	38	2·7	17	0·009	0·006	0·003–0·020	23	3·1	0·5	2·0–4·1
3	Anencephalus	38	2·2	20	0·016	0·006	0·005–0·025	22	3·1	0·4	2·5–3·7
4	Renal anomalies	36	2·4	23	0·01	0·004	0·005–0·016	27	3·2	0·8	2·1–5·6
5	Chondrodystrophies	36	2·5	4	0·01	0·004	0·006–0·015	4	3·5	0·2	3·4–3·8
6	Osteogenesis imperfecta	36	1·9	4	0·007	0·001	0·005–0·008	4	3·2	0·4	2·6–3·5
7	Amniotic fluid leakage	35	1·7	2	—	—	0·012–0·016	2	—	—	2·0–2·4
8	Hydrops fetalis	34	2·1	8	0·013	0·007	0·001–0·021	8	4·4	1·0	3·1–5·6
9	Hydrocephalus	38	3·2	2	0·008	—	0·005–0·011	1	—	—	4·0
10	Meconium peritonitis	37	2·8	1	—	—	0·012	1	—	—	3·8

P value for the differences of the means of each of the groups 2–6 and of group 1 was at least <0·01 for LW:BW ratio and <0·005 for RAC.

group was greater for LW:BW ratio than for RAC. The number of cases with values for both LW:BW ratio and RAC within the normal range is also given. Complementary use of the two criteria failed to detect PH in only a very few cases.

Discussion

Pulmonary hypoplasia is diagnosed in 7·8 to 10·9% of neonatal necropsies and in about half of necropsied neonates with congenital anomalies (Driscoll and Smith, 1962; Pryse-Davies, 1972; Sultana *et al.*, 1973), yet diagnostic criteria of PH have not been established. Whereas histological descriptions of PH have limited value (Potter, 1961; Reale and Esterly, 1973), the RAC provides a simple objective measurement of 'relative paucity of alveoli' or 'crowding of bronchial structures' which is unaffected by the state of expansion of the lungs (Emery and Mithal, 1960). At present PH is usually identified from associated anatomical diagnoses, such as those studied by ourselves. However, the diagnosis is often overlooked, especially when diagnostic associations are lacking. Moreover, a prejudiced diagnosis of PH may be made when anticipated from diagnostic associations.

Our results of LW:BW ratios and RAC are similar to those of Emery and Mithal (1960) when differences in the method (see Materials and Methods) are accounted for (RAC alveolar count = RAC alveolar septal count −1).

While we agree that typical histological changes of PH are due to quantitative rather than to qualitative factors (Reale and Esterly, 1973), we have reservations about anencephalus. We note a discrepancy between the LW:BW ratio and the RAC (Fig. 1a) which is only partially explained by a spuriously low body weight due to absence of the brain. With the exception of cases with associated thoracic skeletal anomalies (Potter, 1961), the pathogenesis of PH in anencephalus has never been satisfactorily explained. This inconsistency between LW:BW ratio and RAC suggests a specific delay in alveolar development, possibly related to the hypothetical role of the pituitary in lung growth (Jain *et al.*, 1973). Animal models of anencephalus produced at 0·6–0·7 of gestation do not appear to have fewer air sacs (Blackburn *et al.*, 1972; Meyrick *et al.*, 1975) but the validity of the model for study of lung growth throughout gestation is questionable.

Necropsy studies of lung development in diaphragmatic hernia are not fully representative of this condition, as patients with less severe PH survive. In survivors there is a tendency towards progressive improvement postoperatively but normal lung function values may never be attained (Chatrath *et al.*, 1971).

In the renal anomaly group the mean values for LW:BW ratio and the RAC were lower than those reported by Reale and Esterly (1973). This is explained by the fact that the latter study included unilateral renal anomalies, which are probably unassociated with PH (Perlman and Levin, 1974).

In our study we showed that PH is the probable cause of death in osteogenesis imperfecta congenita, presumably as a result of restriction of lung growth by the skeletal lesion, as occurs in chondrodystrophies (Finegold *et al.*, 1971). PH was also demonstrated in some instances of hydrops fetalis, as reported by Chamberlain *et al.* (1977), and may have been caused by the thoracic space-occupying effects of large pleural effusions and raising of the diaphragm by tense ascites and gross hepatosplenomegaly. It is suggested that a similar mechanism exists that raises the diaphragm in PH associated with ascites in meconium peritonitis.

There is fairly good agreement of reported normal values of lung weights or LW:BW ratios in different series (0·18–0·022) (Schultz *et al.*, 1962; Potter, 1972; Reale and Esterly, 1973), but by excluding lungs with oedema and exudates, Emery and Mithal (1969) arrived at a mean LW:BW ratio of 0·013. Normal lung weight is greatly influenced by postnatal absorption of lung fluid (Aherne and Dawkins, 1964). In spite of these limitations, an LW:BW ratio <0·012 suggested PH at all gestational ages in our material. This value was outside the range of our normal controls but was higher than half the normal mean (0·009) arbitrarily suggested by Potter (1972) as a criterion of PH. In those instances of PH discovered incidentally, a LW:BW ratio <0·012 led to confirmation of the diagnosis of PH by RAC, and in the light of this diagnosis the clinical and radiological manifestations were retrospectively made more comprehensible.

Data on the number of measurements of each parameter that came within the normal range (Figure) suggest that in each case, the RAC provides a clearer definition between PH and normal subjects than the LW:BW ratio. It should be pointed out that the difference between the mean normal RAC (5·3) and lower limit of normal (4·1) becomes greater when these values are raised to the third power (149 v. 69) in order to produce a 3-dimensional measure (i.e. number of alveoli in terminal respiratory units) from the single dimension that the RAC represents (Emery and Mithal, 1960).

We suggest the following guidelines for the diagnosis of PH. LW:BW ratio <0·009, PH very likely, RAC not obligatory. LW:BW ratio 0·010–0·012, PH probable, RAC indicated for confirmation of diagnosis. LW:BW ratio 0·013–0·017, PH possible, RAC desirable. LW:BW ratio >0·018, PH unlikely, and RAC probably not indicated. Where RAC is estimated, a value <75% of the mean normal value (equivalent to 43% of cubed value) for that laboratory probably indicates PH.

PH is rarely diagnosed in living patients but there is increasing awareness of this condition (Renert *et al.*, 1972; Leonidas *et al.*, 1975). The existence of a spectrum of lung hypoplasia has been recognised but this is not shown in a necropsy study owing to lack of representation of less severe or borderline PH patients who are excluded from study by virtue of their survival (De Lorimier *et al.*, 1967; Burkle and Bravo, 1969; Potter, 1972; Perlman *et al.*, 1975). Finally, the role of impaired lung growth in other neonatal pulmonary conditions—such as hydrops fetalis and even hyaline membrane disease—has not been fully explored.

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Neutrophil function in children with acute lymphoblastic leukaemia in the presence and absence of viral infections

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SUMMARY Neutrophil function was assessed regularly in 26 children with acute lymphoblastic leukaemia (ALL) in remission, both when they were well and during viral infections. Tests of candidacidal ability when these children were apparently free of infection showed a trend towards lower levels compared with controls. The most pronounced depression of candidacidal ability and chemotaxis was during viral infections, and these two functions of neutrophils were more likely to be abnormal then than when the children were free of infection. In children with ALL in remission, whose neutrophils may function abnormally even when they are well, the risk of acquiring bacterial or fungal infections may be made greater by virus infections.

Infection is a major cause of death for children with ALL, particularly during remission (Hughes 1971; Craft *et al.*, 1977). Although viruses are increasingly being incriminated in the deaths of such children, overwhelming bacterial or fungal infections still account for many deaths. Profound neutropenia is not always associated with such deaths. Several of the deaths recently reported from Newcastle were associated with coexistent viral and bacterial infections (Craft *et al.*, 1977). The interaction of such infections is poorly understood. As part of a larger survey of infection and immunity in children with ALL in remission, neutrophil function was assessed to discover whether any defects were detectable and, if so, whether they could be related to the presence of infection.

Patients

Between June 1975 and October 1976, 27 children with ALL presenting consecutively to one of two major hospitals in Newcastle upon Tyne were entered into the study. Their ages at diagnosis ranged from one to 10 years. One patient died before remission was induced. The remaining 26 patients were followed up, while in remission, for periods ranging from 4 months to 2 years. All were receiving a modified version of an ALGB 6801 regimen (Reid *et al.*, 1977). The children were assessed if possible at regular monthly intervals and when infection was suspected. At times, insufficient blood was obtained and some tests could not be performed. Routine testing was not carried out at diagnosis because it was usually impossible to obtain adequate numbers of neutrophils.

Controls

Neutrophil function tests were controlled with cells from laboratory staff. Reference ranges were derived from results obtained from 20 staff members and from 6 children, aged 3 to 11 years, admitted to hospital with noninfective conditions.

Methods

Neutrophils were separated by centrifuging white blood cell-rich plasma from dextran-sedimented blood over a Ficoll-Triosil (Lymphoprep, Nygaard) gradient.

Stimulated nitrobluetetrazolium (NBT) reduction was assessed on whole blood samples by the method of Segal and Peters (1975). Results were expressed as arbitrary spectrophotometer units/10^6 neutrophils.

Chemotaxis was assessed by a method based on that of Wilkinson (1974). Results were expressed as

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the distance in μm travelled by the leading front of neutrophils into the micropore filter.

Killing ability was assessed using *Candida albicans* as the test organism by a method based on that of Goldman and Th'ng (1973). Results were expressed as the percentage of *C. albicans* killed.

Virus infections were diagnosed by immunofluorescent techniques and culture (Gardner and McQuillin, 1974).

During the period of the survey there was no occasion on which adequate numbers of neutrophils were obtained from children with bacterial or fungal infections.

Results

The results of tests of NBT reduction, killing ability, and chemotaxis in the children with ALL, both in the presence and absence of virus infections, are shown in Figs 1, 2, and 3. The reference adult and child

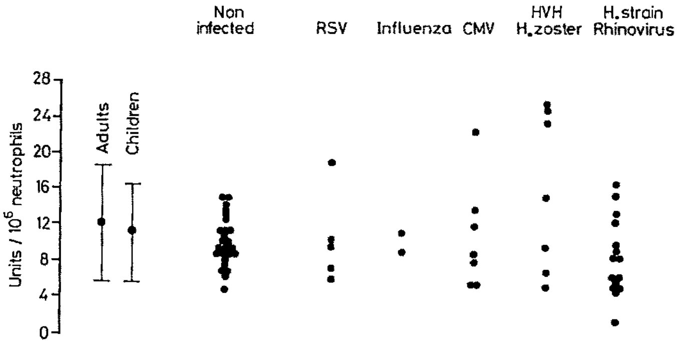

Fig. 1 *Stimulated NBT reduction in children with ALL when well and during virus infections with reference ranges (mean ± SD) for children and adults.*

RSV = respiratory syncytial virus
CMV = cytomegalovirus
HVH = herpesvirus hominis
H. zoster = Herpes zoster

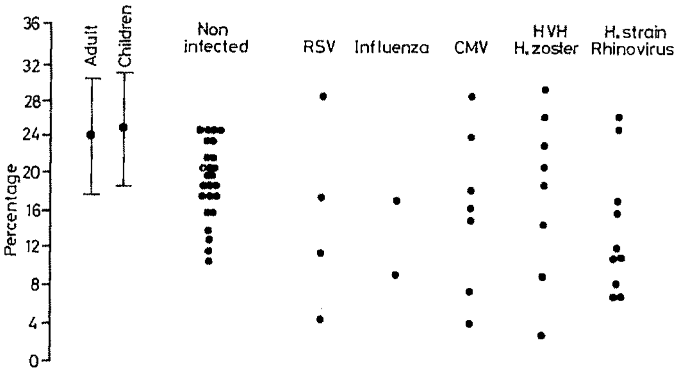

Fig. 2 *Neutrophil candidacidal ability in children with ALL when well and during virus infections, with reference ranges (mean ± SD) for children and adults.*

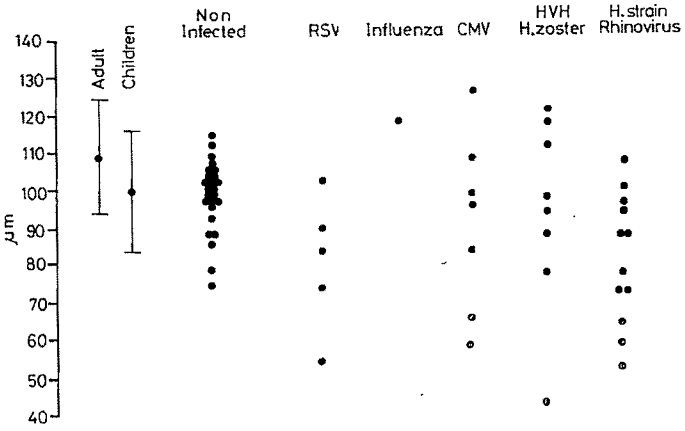

Fig. 3 *Neutrophil chemotaxis in children with ALL when well and during virus infections, with reference ranges (mean ± SD) for children and adults.*

Table 1 *Killing ability. Summary of 'normal' and 'abnormal' results in noninfected and infected children with ALL*

	Noninfected	*Infected*
Normal tests	96	14
Abnormal tests	47	17
Totals	143	31

Table 2 *Chemotaxis. Summary of 'normal' and 'abnormal' results in noninfected and infected children with ALL*

	Noninfected	*Infected*
Normal tests	134	21
Abnormal tests	22	12
Totals	156	33

ranges are given for comparison. Each point in the noninfected group represents a mean of all tests performed in an individual child when no infection could be detected. One of the 26 children was at no time tested when free of infection. All other points represent the results of a single test. The mean value of killing ability (±SD) in the children with ALL when they were free of infection is 19% (±4). The reference adult range is 25% (±6). This difference is significant (Student's t, $P<0\cdot01$).

Tables 1 and 2 give a summary of the results of all the individual tests of killing ability and chemotaxis. Results which are described as 'abnormal' are all below the lowest point on the reference ranges for the appropriate test. Killing ability was more likely to be 'abnormally' low (<18%) in infected than noninfected children ($\chi^2 = 5\cdot3$, $P<0\cdot05$). Chemotaxis was also more likely to be 'abnormal' (<84 μm) in infected children ($\chi^2 = 4\cdot6$, $P<0\cdot05$).

There was no obvious change in the pattern of results with time, nor did the stage of treatment appear to affect them.

Discussion

There was no difference in NBT reduction and chemotaxis between the control populations and the children with ALL when not infected. However the results of tests of killing ability in such children (Fig. 2) suggest there was some impairment, as there was a trend towards lower levels than was found in the normal population. Quantitative assessment of killing ability is simplified if *C. albicans* is used as the test organism. It is probably killed by the hydrogen peroxide mechanism, as are many bacteria.

However, tests of candidacidal ability may not be comparable with those of bactericidal ability. Few defects in neutrophil function during remission of ALL have been reported. Strauss *et al.* (1970) reported a bactericidal defect in 4 of 6 patients in remission. Gregory *et al.* (1972) described a bactericidal defect in a group of children most of whom were in remission. Baehner *et al.* (1973) found a temporary bactericidal defect associated with craniospinal irradiation, but not at any other time in remission. Sarab-el-Nakeeb and Thompson (1977) reported abnormal chemotaxis in children with ALL in remission. Bactericidal defects have also been described during relapse of ALL (Strauss *et al.*, 1970; Humbert *et al.*, 1976).

Depression of neutrophil function by viruses in normal subjects has been demonstrated *in vitro* (Larson and Blades, 1976; Larson *et al.*, 1977; Ruutu *et al.*, 1977). Normal children with virus infections also have abnormally functioning neutrophils (Anderson *et al.*, 1976; Craft *et al.*, 1976). The present study did not show significant depression of NBT reduction in children with ALL by virus infections. However a striking depression of killing ability and chemotaxis in some of these children took place during virus infections.

Virus infections may therefore be associated with depression of neutrophil function in a group of children whose neutrophils may already be adversely affected by their leukaemia or by treatment. This depression of function, in addition to the risks of neutropenia, may make children with ALL even more susceptible to bacterial and fungal infections, and shows the seriousness of comparatively common viruses to such children.

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The following articles will appear in future issues of this journal:

Vertical transmission of hepatitis B surface antigen in carrier mothers in two west London hospitals. *D. Woo, M. Cummins, P. A. Davies, D. R. Harvey, R. Hurley, and A. P. Waterson.*

Non-neuropathic Gaucher disease presenting in infancy. *P. Hodgson, J. Goldblatt, and P. Beighton.*

Childhood cystinuria in New South Wales. Results in children who were followed up after being detected by urinary screening in infancy. *A. Smith, J. S. Yu, and D. A. Brown.*

Nutritional status of light-for-date infants at birth and its influence on early postnatal growth. *D. P. Davies, P. Platts, J. M. Pritchard, and P. W. Wilkinson.*

Numerical evaluation of facial pattern in children with isolated pulmonary stenosis. *H. Ainsworth, J. Hunt, and M. Joseph.*

Infantile hypertrophic pyloric stenosis—unusual familial incidence. *V. R. Finsen.*

Archives of Disease in Childhood, 1979, **54**, 623–625

Intrathecal serotherapy in neonatal tetanus: a controlled trial

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SUMMARY 60 infants with neonatal tetanus were treated at random either by 40 000 units of equine tetanus antitoxin (TAT), intravenously and intramuscularly, or by 40 000 units TAT, IV and IM, plus 150 units of human tetanus immune globulin (TIG) intrathecally. There were 30 infants in each treatment group. Babies were similar in age, sex, weight, incubation period, temperature, and signs and symptoms on arrival at the hospital. The mortality rate, days in hospital, and days of sedation were not significantly different in the two groups.

Tetanus is still a major health problem in developing countries both in incidence and mortality. The mortality is particularly high in neonates (Nourmand *et al.*, 1970; Salimpour, 1977).

Although equine tetanus antitoxin (TAT) has been used to treat this disease for many years, the preferred dose, efficacy, and route of administration are not clear (Brown *et al.*, 1960; Athavale and Pai, 1966). The present tendency is to give a single dose of TAT initially (McCracken *et al.*, 1971). In children 20 000 to 100 000 units have been used (Spaeth, 1941; Brown *et al.*, 1960). It was suggested that intrathecal administration of tetanus immune globulin (TIG) together with corticosteroids reduced the mortality in neonates (Ildirim, 1967, 1974). The purpose of this report is to evaluate intrathecal administration of 150 units of TIG without corticosteroids in the treatment of tetanus neonatorum.

Patients and methods

During the 50-month period from January 1974 to February 1978, 64 newborn infants with the clinical diagnosis of tetanus were admitted to the newborn unit of Nemazee Hospital, Shiraz, Iran. This unit admits all sick neonates from Shiraz and the surrounding area, altogether a population of about 600 000. The diagnosis was made clinically by M.R.S.

All newborn babies in this prospective study were alternately assigned to one of two treatment groups. The control group received 20 000 units of TAT IV and 20 000 units IM in the first few hours after admission. The study group received the same amount of TAT by the same routes, plus 150 units of TIG intrathecally.

Blood cultures and spinal taps were performed in both groups of babies.

Valium (15 mg/kg per day) was given initially intravenously and then by nasogastric tube. If the valium failed to control the convulsions, chlorpromazine (Largactil) 2–3 mg/kg per day was added.

Initially, all babies were given benzylpenicillin 50 000 to 100 000 units/kg per day and gentamicin 5 to 6 mg/kg per day in two divided doses. Benzylpenicillin was continued for 10 days, but gentamicin was stopped after 5 days if the spinal fluid and blood cultures remained negative.

Each infant was admitted to a separate room. The umbilical area was thoroughly cleaned. Nasogastric tube feeding was initiated as soon as the baby's convulsions were under control.

Age, sex, weight, incubation period, rectal temperature, clinical symptoms, and signs of pneumonia were recorded for each baby at the time of admission. Days in hospital, days to death, days of sedation, and mortality for both treatment groups were recorded.

Results

Of 64 neonates with the clinical diagnosis of tetanus, 60 were admitted to the trial, 30 in each treatment group. Four patients were excluded within the first 3 days: 2 because of associated meningitis and 2 because they had received some TAT before arrival at the hospital.

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All infants had been delivered at home with the help of unqualified midwives. 14 (23%) of 60 were from Shiraz and the rest came from villages nearby.

There were 2 preterm babies and one term small for gestational age (SGA) infant in the control group, and one term SGA infant in the study group. Table 1 shows the main signs and symptoms in these babies on admission. Table 2 compares various characteristics in the two groups.

The two groups were comparable for sex, age, weight, incubation period, temperature on admission, days in hospital, days of sedation, days to death, and number dying. There was no significant difference in survival rate between the two groups.

There were 2 babies, one in each group, who recovered from tetanus but died from other causes. One died 60 days after admission from gastroenteritis, urinary tract infection, and hydronephrosis and the other baby died 30 days after admission from hepatitis and septicaemia. The days to death for these 2 patients are excluded from the analysis.

Table 1 *Signs and symptoms in both groups of babies on admission*

Signs and symptoms	*Study group*	*Control group*	*Total (n = 60)*
Refusal to feed	29 (97)	29 (97)	58 (97)
Convulsion (tetanic spasm followed by clonic movement)	28 (93)	28 (93)	56 (93)
Trismus	27 (90)	26 (87)	53 (88)
Generalised rigidity on arrival	28 (93)	22 (73)	50 (83)
Cyanosis	18 (60)	20 (67)	38 (63)
Irritability	18 (60)	16 (53)	34 (57)
Respiratory distress	17 (57)	12 (40)	29 (48)
Opisthotonus on arrival	15 (50)	14 (47)	29 (48)
Poor reflexes	5 (17)	5 (17)	10 (17)
Risus sardonicus	2 (7)	2 (7)	4 (7)

Percentages are given in brackets.

Table 2 *Summary of various characteristics of the two groups*

Characteristics	*Study group (n = 30)*	*Control group (n = 30)*
Mortality	13 (43)	15 (50)
Age on admission (days)	9·5 ± 8·5*	8·9 ± 7·8*
Sex		
Male	26 (87)	25 (83)
Female	4 (13)	5 (17)
Weight (g)	3025 ± 906*	2878 ± 995*
Incubation periods		
<7 days	22 (73)	21 (70)
8–14 days	8 (27)	9 (39)
Rectal temperature on admission		
<37·5°C	13 (43)	13 (43)
37·6–39·0°C	11 (37)	11 (37)
>39·1°C	6 (20)	6 (20)
Days in hospital for survivors	26·7 ± 19·6*	26·8 ± 28·5*
Days sedated for survivors	21·8 ± 12·7*	25·2 ± 14·4*
Days to death	5·2 ± 7·3*	6·4 ± 10*

Percentages are given in brackets.
*Mean ± 2 SD.

Table 3 *Mortality rate according to incubation period*

Incubation period	*Study group (n = 30)*	*Control group (n = 30)*
Up to 7 days	11/22 (50)	13/21 (62)
8–14 days	2/8 (25)	2/9 (22)
Total mortality	13 (43)	15 (50)

Percentages are given in brackets.

The mortality rate according to incubation period is shown in Table 3. The death rate for incubation periods less than 7 days was slightly higher in the control group, 13 (62%) of 21, than in the study group, 11 (50%) of 22.

There were 12 (40%) of 30 babies in the study group and 8 (27%) of 30 in the control group who showed some sign of pneumonia on admission.

Discussion

The intrathecal administration of TAT for treatment of tetanus began early in the 20th century. The first trial was by von Leyden in 1901, and then there were trials by Penna in 1902 and Rogers in 1905. Because of fatal complications of intrathecal TAT administration and no obvious change in survival rates, this treatment was stopped (Dietrich, 1940; Pratt, 1945).

Ildirim (1974) used intrathecal TAT or TIG, combined with corticosteroids, with good results in tetanus neonatorum. At the Fourth International Congress on Tetanus in 1975, it was felt that serious consideration should be given to this method of treatment (Furste, 1976). The amount recommended was a single injection of 250 units of TIG mixed with 12·5 mg prednisolone, given intrathecally. 2500 units of TAT were given both IM and IV, plus 10 mg prednisolone in two divided doses orally. A mortality rate between 14·8 and 20% was reported (Ildirim, 1974). However, the relative importance of each component of this treatment remained to be established. Therefore, we used intrathecal TIG without corticosteroids, choosing a dose of 150 units because we were giving 40 000 units of TAT by other routes. The results in the study group showed no advantage in this treatment (Table 2).

As intrathecal TIG did not alter the mortality rate for this disease, good results in other studies may be attributed to corticosteroids, to a higher dose of intrathecal TIG, or possibly, to synergism. A controlled trial of intrathecal corticosteroids without TIG is now in progress.

Any conclusion about therapy must be guarded since Chen (1974) showed that good nursing care can reduce the mortality rate to 20%.

I should like to thank Dr Paul A. Steinman for his useful suggestions and guidance in the preparation of this report, and Dr A. Madani for collecting some of the data.

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Readers should see related correspondence on pages 650–651.

Archives of Disease in Childhood, 1979, **54**, 626–634

Current topics

A suggested child-health clinic form

R. S. ILLINGWORTH

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After more than 30 years' experience of baby clinics, first in an obstetrics hospital and more recently in Area Health Authority clinics, I am convinced that there is a need for a suitable form for the use of clinic doctors and health visitors, and for family doctors who have their own child health clinics. I believe that the form I have designed provides a good basis.

The assessment, and the form recording it, must be simple and practical. An assessment which takes about 30 minutes is certainly necessary in special circumstances if there is difficulty in the diagnosis, but it is impractical in a busy clinic with babies and children awaiting immunisation, or assessment, or both. Hence all irrelevant developmental features—interesting as they are, and sometimes important for difficult cases—must be eliminated. Milestones and tests should be strictly confined to those that matter, those which are extremely unlikely to miss any significant abnormality.

As in a passport form, application for life insurance, or VAT assessment form, each question must be answered and so must be capable of being answered. For instance, it is useless in the 6-week assessment to include the word 'reflexes', as is currently done in a commonly used form; the clinic doctor cannot be expected to know which of the 70 or so primitive reflexes is relevant, and he therefore has to decide whether to insert a 'yes' or 'no', or a tick or a cross. He almost always inserts a tick, hardly an informative answer.

In a much used school clinic form, there is the heading:

Development, hernia	☐
Other	☐
Psychological development	☐
Stability	☐

Children's Hospital, Sheffield
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In my form, there are spaces with headings which anyone can understand: they are 'normal', 'doubtful', 'abnormal', with a space for explaining why the finding may be abnormal.

I have left no space for an overall score, in the form of a figure. Some features of a child's development—especially his alertness, responsiveness, and interest in surroundings—are much more important than others. It is not the place of a clinic doctor to attempt to calculate an IQ score: but he is required to separate the normal from the abnormal, to detect the child who calls for special investigation by an expert. I have avoided defining the range of normal, for it is never possible to insert the exact dividing line between normal and abnormal.

I have sketched the principal features of motor and manipulative development because many doctors and health visitors like to have such a guide (Illingworth, 1977). For the same reason I have given the average age at which milestones are reached, using Gesell's figures. For further information about these see Illingworth (1979).

My intention is that all the information will go on a 6-sided firm card, similar to the one now often used in clinics. I would welcome suggestions for its improvement, but the form must not be lengthened.

Permission was obtained from Blackwell Scientific Publications for reproduction of the sketches.

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Health record (first 5 years)

Surname: (block letters) Christian names:

Date of birth	*Mother married or single* *M/S*	*Where born*	*Sex* *M/F*	*Birthweight* *(kg)* *(lb)*	*Head circumference* *(cm)* *(in)*	*Duration of gestation*

Address	*Telephone:*	*Doctor's address*	*Telephone:*
1		1	
2		2	
3		3	
4			

Parents: year of birth	*Occupation*		*Health*	*Relevant illness, especially genetic*
	Past	*Present*		
Mother				
Father				

	Child alive year of birth	*Special illness or handicap*	*Miscarriage (year)*	*Stillbirth (year)*
Previous pregnancies				
1				
2				
3				
4				

Risk factors
i.e. Rubella
Other infection in pregnancy
Blood group incompatibility
APH
Diabetes
Toxaemia
Drugs in pregnancy
Other illness

Birth
- Vertex
- Breech
- Caesarean

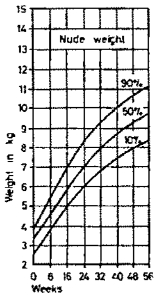
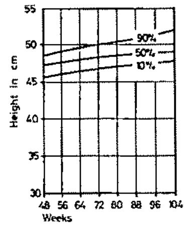
Condition at birth
- Anoxia
- Other

Treated in intensive care unit

Newborn period
Apnoeic attacks
Congenital abnormalities
Other

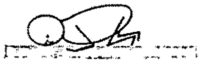
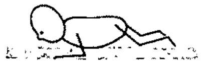
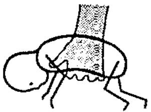
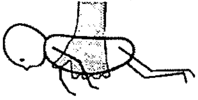
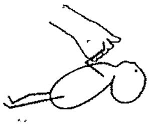
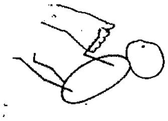
Immunisation	*Date*			*Booster*	*Significant reaction*
	1	*2*	*3*		
DPT					
DT					
Polio					
BCG					
Measles					
Hearing test					

6 weeks (corrected age: prematurity allowed for)

Date	*Number of days after birth*	* *Weight* (*kg*) (*lb*)	*Head circumference* (*cm*) (*in*)	
Feeding Breast Modified dried milks Measures of powder Water Number per day Other foods				

History
Any problems (e.g. crying, sleep, feeding, vomiting)

Developmental history	*Smiling in response to mother (average 4–6 weeks)*	*If +, say age it began*	*Doubtful*	*No*

Examination		*Normal*	*Doubtful*	*Abnormal*	*If doubtful or abnormal, in what way?*
Interest, alertness, responsiveness					
Eyes (look for nystagmus, opacity, persistent squint)					
Development prone	 Newborn  6 weeks				
Ventral suspension	 Newborn  6 weeks				
Pulled to sit	 Newborn  8 weeks				

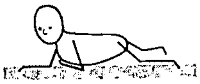
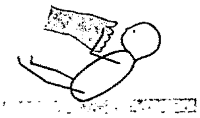
* As differences in weight between boys and girls are so slight only one chart is necessary.

Examination	*Normal*	*Doubtful*	*Abnormal*	*If doubtful or abnormal, in what way?*
Neurological examination (e.g. tone—exaggerated knee jerks, persistent ankle clonus, hypotonia, hypertonia)				
Back (look for congenital dermal sinus)				
Mouth (no thrush)				
Heart				
Abdomen				
Umbilicus				
Hip, abduction				
Testes—descended or will descend				
Skin				
Overall opinion				

Action taken
i.e. Letter to GP
to hospital
Why?
Extra appointment (date)
Note for health visitor

Intermediate

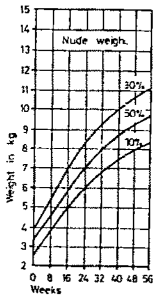
Date

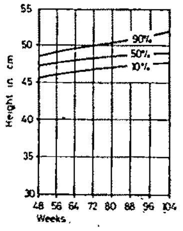
Milestones		*Normal*	*Doubtful*	*Abnormal*
i.e. Prone	 3 months			
Pulled to sit, no head lag	 4 months			
Turns to sound (average 3–4 months) on level with ear				
Plays with rattle—placed in hand (average 3–4 months)				
Reaches for and gets object not placed in hand (average 5 months)				

6 months (corrected age: prematurity allowed for)

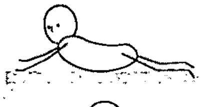
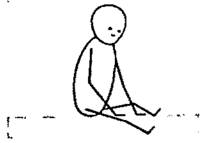
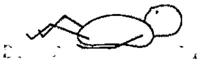
Date	*Age (weeks)*	*Weight* *(kg)* *(lb)*	*Head circumference* *(cm)* *(in)*

History
Any problems (e.g. crying, sleep, feeding, vomiting)
Any illness?





Developmental history	*If +, say age it began*	*Doubtful*	*No*
Turns to sound (average 3–4 months)			
Reaches and gets objects (not placed in hand) average 5 months			
Chews (not sucks) average 6 months			

Examination	*Normal*	*Doubtful*	*Abnormal*	*If doubtful or abnormal, in what way?*
Interest, alertness, responsiveness				
Eyes (as before)				
Sees pellet or cube				
Development				
Prone  6 months				
 6 months				
Supine, head up spontaneously  6 months				
Reaches and gets object				
Right				
Left				
Transfers object one hand to another (average 6 months)				
Weight on legs, held standing				
Neurological (e.g. tone; hypotonia or hypertonia)				
Hearing				
Right				
Left				
Mouth (look for thrush)				
Heart				
Abdomen				
Hips (abduction)				
Testes (as before)				
Skin				
Overall opinion				

Action taken
i.e. Letter to GP
to hospital
Why?
Extra appointment (date)
Note for health visitor

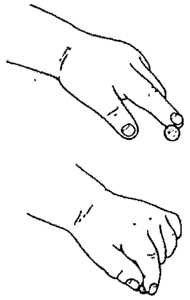
Intermediate
Sit for seconds on floor, no support (average 32 weeks)

10–12 months (corrected age: prematurity allowed for)

Date	*Age (months)*	*Weight* *(kg)* *(lb)*

History
Any problems (e.g. crying, sleep, feeding, vomiting, sphincter control)
Any illnesses?

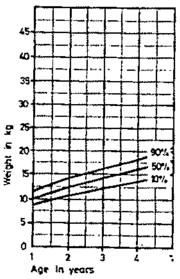
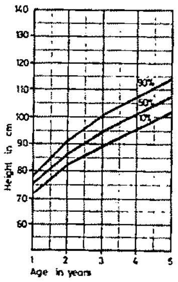
Developmental history	*If +, give age it began*	*Doubtful*	*No*
Sits on floor for seconds, no support (average 7 months)			
Crawls on abdomen (average 9 months)			
Creeps, hands and knees (average 10 months)			
Walks, holding on to furniture (average 11 months)			
Chews (average 6 months)			
Bye-bye, pat-a-cake (average 9 months)			
Helps dress (arm out for coat, foot for shoe) (average 10 months)			
Words with meaning (average 12 months)			

Examination	*Normal*	*Doubtful*	*Abnormal*	*If doubtful or abnormal, in what way?*
Interest, alertness, responsiveness				
Eyes (as before)				
Developmental				
Grasp right				
Grasp left				
Index finger approach				
 9–10 months				
Pellet between tip of forefinger and tip of thumb (both average 10 months)				
Crawls or creeps				
Full weight on legs				
Neurological (e.g. tone, hypotonia, or hypertonia)				
Hearing				
Right				
Left				
Mouth				
Heart				
Abdomen				
Hips				
Testes				
Skin				
Overall opinion				

Action taken
i.e. Letter to GP
to hospital
Why?
Extra appointment (date)
Note for health visitor

Intermediate milestones (average)			
Tower of 2 one-inch cubes	15 months	No more casting or mouthing of objects	15 months
Tower of 3-4 one-inch cubes	18 months	Takes shoes, socks off	15 months
Tower of 5-6 one-inch cubes	21 months	Domestic mimicry	15 months
Walks no help	13 months	Tells mother he wants pot	18 months
Manages ordinary cup, picks it up, drinks, puts it down (no help)	15 months	Points to 2-3 parts of body on request	18 months

2 years

Date	*Age (years and months)*	*Weight* *(kg)* *(lb)*	*Height* *(cm)* *(in)*
History Any problems (e.g. crying, sleep, eating, vomiting, sphincter control) Any illnesses?			

Developmental history	*If +, give age it began*	*Doubtful*	*No*
Dry by day (average 2 years) Joins 2-3 words together (average 21-24 months) Puts shoes, socks, pants on (average 2 years)			

Developmental examination only if necessary	*Normal*	*Doubtful*	*Abnormal*	*If doubtful or abnormal, in what way?*
Tower of one-inch cubes (averages 6-7) Imitates drawing of vertical line and circle Points to 4 parts of body on request				
Examination Interest, alertness Speech Eyes (as before) Appears to see normally Hearing Right Left Heart Abdomen Testes Skin Overall opinion				

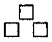
Action taken
i.e. Letter to GP
to hospital
Why?
Extra appointment (date)
Note for health visitor

Intermediate
Tower of 8 one-inch cubes (2½ years)
Imitates vertical and horizontal stroke (in drawing)
Digits (e.g. say after me 7-9) 2 in 1 of 3 trials

3 years

Date	*Age (years and months)*	*Weight* *(kg)* *(lb)*	*Height* *(cm)* *(in)*

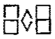
History
Any problems (e.g. crying, sleep, eating, sphincter control)
Any significant illnesses?

Developmental history	*If +, give age it began if relevant*	*Doubtful*	*No*
Dry by day			
Dry by night (average 3 years)			
Dresses self fully (except buttons, shoe laces) (average 3 years)			
Developmental examination only if necessary			
Tower of one-inch cubes (average 9-10) Note tremor or ataxia			
Imitates bridge (i.e. make bridge, letting him see you do it) 			
Copies circle from card			
Imitates drawing of a cross + (i.e. let him see you do it)			
Digits, average 3 in 1 of 3 trials			

Examination	*Normal*	*Doubtful*	*Abnormal*	*If doubtful or abnormal, say in what way*
Interest, alertness, responsiveness				
Speech				
Eyes				
Hearing				
Right				
Left				
Heart				
Abdomen				
Testes				
Skin				
Overall opinion				

Action taken
i.e. Letter to GP
to hospital
Why?
Extra appointment (date)
Note for health visitor

Intermediate
3½ years Copies bridge of cubes (i.e. does not see it made)
Digits 3 (2 of 3 trials)
4 years Can button clothes
Imitates gate (i.e. sees it made)



Copies + (cross) from card.

4½ years

Date	*Age (years and months)*	*Weight* *(kg)* *(lb)*	*Height* *(cm)* *(in)*

History
Any problems?
Any illnesses?

Developmental history	*If +, say when it began (if relevant)*	*Doubtful*	*No*	
Dry by day				
Dry by night				
Developmental examination only if necessary				
Copies gate (note tremor, ataxia)				
Copies square				
Digits 4 (1 of 3 trials)				

Examination	*Normal*	*Doubtful*	*Abnormal*	*If doubtful or abnormal, say in what way*
Interest, alertness				
Speech				
Eyes				
Hearing				
Right				
Left				
Heart				
Abdomen				
Testes				
Skin				
Overall opinion				

Action taken
i.e. Letter to GP
to hospital
Why?
Extra appointment (date)
Note for health visitor

Subsequent
5 years copies triangle △
Digits 4 (2 of 3 trials)
ties shoes laces
6 years copies diamond ◊
Imitates steps of 10 cubes

Archives of Disease in Childhood, 1979, **54**, 635–647

Short reports

Neonatal small left colon syndrome

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SUMMARY Five patients with neonatal small left colon syndrome are described together with some early investigative studies on rectal biopsy material. Current reports on this condition are reviewed. The precise aetiology remains unknown, but vigilance and early referral are recommended in view of the several reports of colonic perforation.

Delay in diagnosis and treatment can result in serious complications in the otherwise benign neonatal small left colon syndrome. This condition was first distinguished from other forms of microcolon by Davis *et al.* (1974), and subsequently reports have suggested a surgical orientation. The condition presents as a low obstruction of the large bowel, similar to Hirschsprung's disease in the newborn. There is failure to pass meconium, with tympanitic distention of the abdomen and bilious vomiting.

Contrast radiography, particularly with Gastrografin, shows a smooth, narrow sigmoid and descending colon, with proximal dilatation of the large bowel. However, the enema also promotes both the rapid evacuation of meconium and the early establishment of normal defecation. Many of the mothers of such babies have diabetes mellitus.

A group of 5 babies illustrates the practical management of the condition; 2 of them are described in detail.

Case reports

Case 1. A baby boy, weighing 2·65 kg, delivered normally at 37 weeks. There was no history of maternal diabetes. He failed to pass meconium and was transferred at 30 hours with tympanitic abdominal distention and bile-stained vomiting.

Plain *x*-rays of the abdomen showed dilated loops of small and large bowel, with multiple fluid levels consistent with a low obstruction of the large bowel (Fig. 1). A Gastrografin enema was performed to assist radiological diagnosis. This showed a smooth, narrow descending and sigmoid colon with a marked 'transition zone' to distention at the splenic flexure (Fig. 2). The colon proximal to the splenic flexure was overfilled with air and meconium. These appearances are typical of the neonatal small left colon syndrome but simulate long-segment Hirschsprung's disease. The latter diagnosis was made in error, and a left transverse colostomy established. Subsequent investigations showed no evidence of Hirschsprung's disease and at 11 months the colostomy was closed. The infant has remained well since.

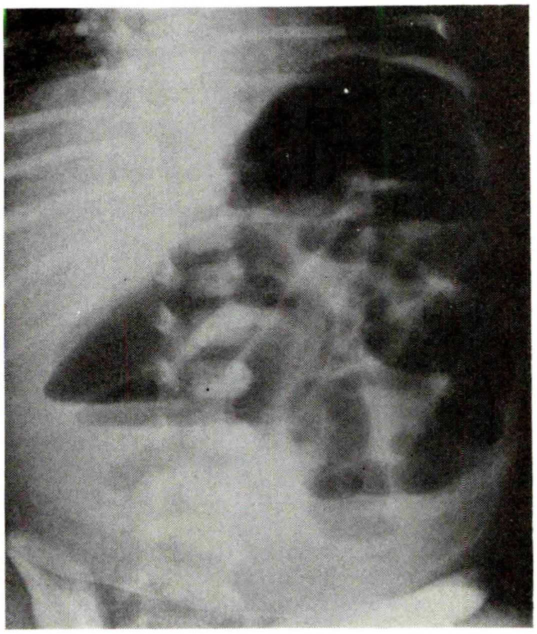

Fig. 1 *Erect abdominal x-ray showing multiple fluid levels in dilated small and large bowel.*

Case 2. A baby girl weighing 3·4 kg of a diabetic mother, delivered by forceps at 36 weeks' gestation. She was referred at 24 hours with failure to pass

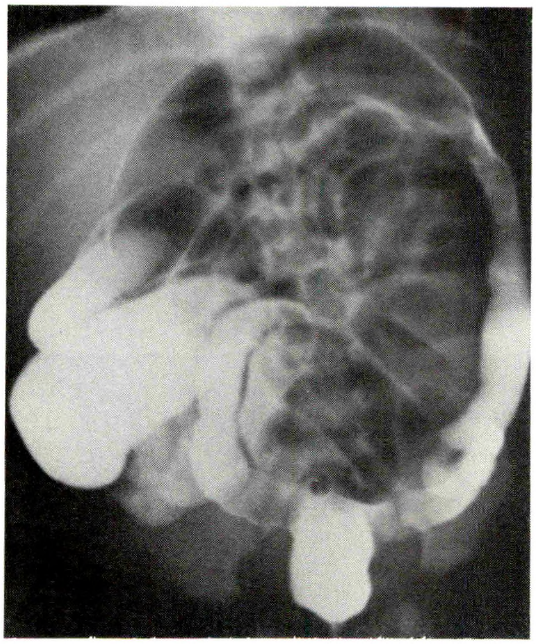

Fig. 2 *Gastrografin enema showing narrowed descending and sigmoid colon and transition zone at splenic flexure.*

meconium, tympanitic abdominal distention, and bile-stained vomiting. Plain *x*-rays indicated a low colonic obstruction and a Gastrografin enema showed the typical appearances of the small left colon syndrome.

Evacuation of meconium followed rapidly and subsequent bowel function was normal. No further investigations were made and the baby has remained well.

Three other infants were seen in whom the history and progress were similar to Case 2, although none was known to have a diabetic mother. Further description of the clinical details is redundant but the results of investigations undertaken to exclude Hirschsprung's disease are of interest.

In Case 1 quantitative estimations of total cholinesterase activity were made in rectal biopsy specimens, using the method described by Boston *et al.* (1975). At 72 hours, the value was in the high normal range (21·8 rate units) and barely excluded Hirschsprung's disease but, when it was repeated at 2 weeks, the result was unequivocally normal (10·0 rate units). In 2 of the other patients, estimations were done for total cholinesterase and acetyl cholinesterase, using the method described by Dale *et al.* (1977). In one, the results were normal at 4 days, but in the other patient, in whom the quantity of enzyme present was also normal, the ratio of acetyl cholinesterase to total cholinesterase was 82% which is consistent with Hirschsprung's disease. This estimation was performed at 3 days, but repetition was not justified in view of the patient's good progress.

Discussion

Sluggish or delayed passage of meconium in the newborn is well recognised, and there are various reasons for this condition. Two of the causes to be distinguished from the small left colon syndrome are the meconium plug syndrome (Clatworthy *et al.*, 1956), and long segment Hirschsprung's disease.

The small left colon syndrome is distinct from either as there is no meconium plug and the intrinsic neurohistology of the affected bowel is apparently normal. In the first description of the syndrome (Davis *et al.*, 1974) 20 infants were reported, 2 of whom were operated on as suspected of having Hirschsprung's disease. One other patient died soon after birth of hyaline membrane disease. After administration of a diagnostic barium enema, all the remaining 17 patients began and continued to evacuate their bowels normally. Eight of them had diabetic mothers and this high correlation has subsequently been confirmed (Davis and Campbell, 1975; Philippart *et al.*, 1975; Stewart *et al.*, 1977). Later reports have not agreed with the initial opinion that complications are rare. Philippart *et al.* (1975) and Stewart *et al.* (1977) reported that in 4 babies out of 12 there were perforations of the bowel. These perforations are often in the caecum and, in one baby, this was 6 days after a barium enema. For this reason vigilance is recommended before *x*-ray examination with contrast enemas is undertaken, and early referral of these patients to paediatric surgical centres for diagnosis and treatment is to be preferred.

The aetiology of the small left colon syndrome is obscure. No abnormality of meconium has so far been shown and it is unusual for a meconium plug to be passed (Clatworthy *et al.*, 1956; Ellis and Clatworthy, 1966).

Davis *et al.* (1974) reported that in biopsy material from 4 babies increased numbers of immature small cells were noted in the myenteric plexus, and these were present in both the narrow and dilated areas of colon. These findings were confirmed by Stewart *et al.* (1977) but not by Philippart *et al.* (1975), and none of the biopsy material now reported has shown any gross abnormality in the intramural ganglion cells and nerves, but studies of the cholinesterase suggest a temporary ganglion cell dysfunction.

Philippart *et al.* (1975) confined their attention to the children of diabetic mothers and suggested that the problem in the infant results from impaired intestinal motility, possibly promoted by glucagon, rather than from an intraluminal plug. In several of their patients an element of obstruction persisted after complete evacuation of meconium and it has been shown that the small calibre of the left colon can persist for variable periods despite normal bowel activity (Davis *et al.*, 1974). Their hypothesis is that an increase in glucagon excretion occurs in babies in the perinatal period either secondary to hypoglycaemia associated with maternal diabetes in a complex way, or with stress. Glucagon is known to decrease bowel motility in the jejunum and sigmoid colon. Conversely hypoglycaemia can also increase bowel motility by vagal and sympathetic stimulation, and consequently Stewart *et al.* (1977) have proposed that the immature small intramural nerve cells are unable to respond to increased sympathetic stimulation. The results of further studies are awaited.

I wish to thank Mr J. E. S. Scott and Mr J. Wagget, consultant paediatric surgeons, for permission to study their patients.

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Acute necrotising fasciitis due to streptococcal infection in a newborn infant

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SUMMARY A 3-day-old baby girl developed septicaemia, meningitis, and necrotising fasciitis due to group A β-haemolytic streptococcus, type M52, which was also cultured from the mother's cervix. Necrotising fasciitis is a severe infection of the skin and subcutaneous tissues with infarction, necrosis, and sloughing of the affected areas. Early recognition of this condition is essential so that appropriate treatment can be given.

Acute necrotising fasciitis is a rare but severe bacterial infection of the subcutaneous tissue and fascial planes, producing extensive destruction of tissues (Hammar and Wagner, 1977). It is often associated with blood stream invasion by the causative pathogen, and the mortality is high. The condition is familiar to the surgeon, but it appears to be rare in children (Wilson and Haltalin, 1973), and only 3 cases have been reported in newborn infants (Weinberger *et al.*, 1972; Ramamurthy *et al.*, 1977).

We report a newborn infant who developed septicaemia, meningitis, and necrotising fasciitis caused by group A β-haemolytic streptococcus.

Case report

A term baby girl of 2·7 kg was born to healthy non-related parents after a pregnancy complicated only by a heavy leucorrhoea during the 3rd trimester. The membranes ruptured spontaneously 14 hours before a normal delivery. The Apgar score at one minute was 9, and the initial examination was normal. On the 3rd day of life it was noted that she nursed poorly, and an erythematous lesion was observed on the right cheek. Within a few hours the baby's condition deteriorated. She became apathetic, comatose, and her rectal temperature rose to 39·5°C. The rash had spread to the scalp, the back of the neck, and the left upper arm. Initially the rash was indurated, erythematous, and warm. No regional lymphadenitis was noted. A severe infection was suspected.

The blood count showed a leucopenia of $1\cdot 5 \times 10^9$/l and a thrombocytopenia of $55\cdot 0 \times 10^9$/l. The next day the leucocyte count increased to $29\cdot 6 \times 10^9$/l with 39% band cells and 5% metamyelocytes. Chest *x*-ray and urine analysis were normal. The spinal fluid was bloody. Cultures from the nose, skin, CSF, blood and from the mother's cervix grew β-haemolytic streptococcus group A, type M52. A repeat lumber puncture 2 days later showed clear CSF with cells $0\cdot 028 \times 10^9$/l (mainly polymorphonuclears), a protein level of 220 mg/100 ml (2·2 g/l), and glucose of 47 mg/100 ml (2·6 mmol/l). The culture was negative.

Treatment was immediately started with IV penicillin, gentamicin, and chloramphenicol, and a double volume exchange transfusion was performed. When the results of the cultures were received treatment was continued with only penicillin and frequent transfusions of blood and plasma.

The infant's condition improved rapidly. She became alert and responsive. However, the skin rash changed to a dusky bluish-grey colour, vesicles appeared, and the rash spread along the fascial planes of the upper arm. Subsequently the skin became a purplish colour in some areas and extremely indurated (Fig. 1). The same process was seen in the neck but the rash on the right cheek and the scalp faded.

Gradually areas of necrosis appeared on the skin of the neck and left upper arm and the skin sloughed (Fig. 2). Debridement was performed and the skin was treated with dilute solutions (0·5%) chlorinated lime and boric acid solution (BPC) dressings. Granulation tissue appeared very slowly and it was therefore decided to treat the skin of the arm with pig skin treated with glutaraldehyde. There was rapid growth

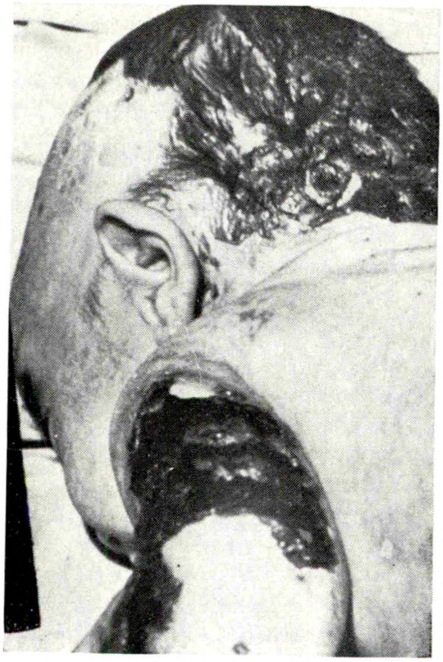
Fig. 2 *Necrotic areas of skin on left upper arm.*

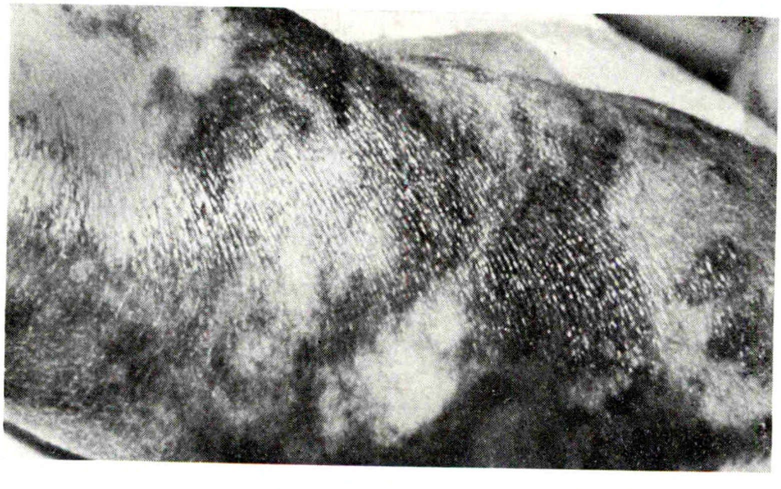
Fig. 1 *Lateral view of left upper arm showing the marked induration of the skin with areas having a purplish-black colour.*

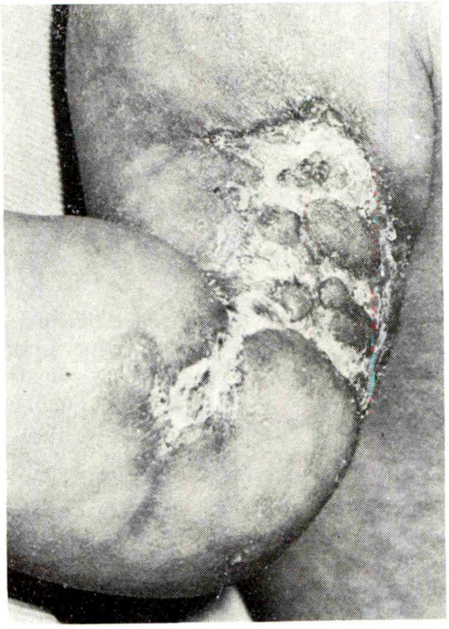

Fig. 3 *Scarring and cicatrisation of skin on left upper arm.*

of granulation tissue and the skin healed with good scarring (Fig. 3). No side effects were noted from the treatment with boric acid solution. The infant was discharged at age 2 months in good health; she was neurologically normal.

Discussion

Streptococcal septicaemia in neonates is usually associated with strains of Lancefield group B. Although no longer the scourge of maternity units, group A streptococci can still cause severe neonatal infection (Peter and Hazard, 1975). The infant may be infected by the mother who carries the streptococcus in her respiratory tract or in her vagina, as was the case in this infant, or by hospital staff.

Group A streptococcus is the most common cause of necrotising fasciitis, although other Gram-positive or Gram-negative organisms have also been reported. Joseph Jones (1871), an army surgeon during the American Civil War, first described this condition. Meleney (1933) gave a clear description of it. The area first becomes swollen, erythematous, warm, and painful. Unlike erysipelas, the border is not raised or well defined and the development of lymphangitis or lymphadenitis is unusual. The overlying skin develops a dusky bluish-grey colour and vesicles may appear. Fluid aspirated from these vesicles may be clear or turbid and usually contains the infecting organisms. The infection spreads rapidly along the fascial planes producing thrombosis of nutrient vessels with resultant necrosis of the overlying subcutaneous tissue and sloughing of the skin. Although the infection usually begins in an operative wound, it may develop without any apparent cause. Unchecked the process spreads rapidly, leading to debility, septicaemia, metastatic abscess, and death.

Therapeutic success depends on prompt recognition of the syndrome, early isolation of the infecting organism, treatment with appropriate antibiotics, vigorous debridement of superficial necrotic tissue, and incision of deep fascia to drain the underlying exudate. Supportive therapy with frequent transfusions of blood and plasma is essential. In our patient there was a rapid response to antibiotic treatment and the infant's general condition greatly improved. After debridement there was, however, very little granulation tissue formation and it was necessary to cover the area of the left upper arm with porcine skin. This resulted in rapid formation of granulation tissue and cicatrisation of the wound.

The infant was discharged at age 2 months, and at one year was found to be normally developed.

We thank Dr S. Rabinowitz, Streptococcus Reference Laboratories of the Ministry of Health, for the typing of the bacterial strains.

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Subacute sclerosing panencephalitis after drug-induced immunosuppression

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SUMMARY A girl developed subacute sclerosing panencephalitis (SSPE). Eight years earlier she had had measles infection contracted shortly after cytotoxic treatment and radiotherapy for a spinal neuroblastoma. The case illustrates that typical SSPE, like immunosuppressive measles encephalopathy, can arise after drug-induced immunosuppression, and supports the view that these diseases probably represent opposite ends of a spectrum induced by measles virus infection in an individual with some form of immunological deficiency.

Immunosuppressive measles encephalopathy (IME) is the term suggested by Pullan *et al.* (1976) for the rapidly progressive form of measles encephalitis in children who contract measles during immunosuppressive treatment. The neurological disorder develops 5 weeks to 6 months after measles infection and was first described by Lyon (1972). One way in which subacute sclerosing panencephalitis (SSPE) differs is that the interval between measles and the encephalopathy is much longer (average 6·6 years, Bellman and Dick, 1977) and we have found only one account of an SSPE-like illness after immunosuppressive treatment (Loirat *et al.*, 1971). We report a girl who contracted measles shortly after having received cyclophosphamide and radiotherapy for a neuroblastoma and who developed typical SSPE 8 years later.

Case report

The girl, born in Morayshire in July 1967 after an uneventful pregnancy and labour, developed paraplegia in November 1967 due to an extradural neuroblastoma at T9. She was in Adelaide, South Australia, at that time and after surgical decompression of the cord, a course of radiotherapy totalling 3500 rads was administered to a field extending from T7 to L4 inclusive. Cyclophosphamide was given in a dose of 3 mg/kg per day from 18 March to 27 August 1968. Treatment was interrupted twice for short periods because of neutropenia and was finally stopped owing to recurrence of neutropenia and anaemia. In late September she contracted measles from her elder sister but the illness was mild. She had not had measles immunisation.

The family returned to the UK in 1969. The patient's paraplegia was permanent and an ileal diversion was fashioned in 1971 because of urinary incontinence. Cycloserine 125 mg daily was given from 1971 to 1977 prophylactically for urinary tract infection.

In June 1977 the girl was referred to the neurology clinic because of deterioration in school performance, and lack of co-ordination and dressing skills during the previous 4 months; before this she had made good progress at school and had walked well with the aid of crutches and calipers. The only abnormality found apart from the paraplegia was slight incoordination of the left hand. The fundi were normal. When seen in August the patient was found to have suffered further deterioration in intellectual function and was reported to have had brief 'absences' accompanied by drooping of the left side of her mouth and a tendency to fall to the left. Her left arm now had a slight tremor and was weak. Treatment with sodium valproate was begun. In October she was admitted to hospital and by then had deteriorated markedly with spasticity of both upper limbs, especially the left, myoclonic jerks on this side, and epilepsia partialis continua of the left arm and left side of the face. She died 3 weeks later, 8 months after her initial symptoms.

Investigations

Urine (July 1977) vanillylmandelic acid and catecholamines normal: 17-hydroxycorticosteroids 20 µmol/24 h (5·8 mg/24 h), 17-ketosteroids 9 µmol/24 h (2·6 mg/24 h). Skull and chest *x*-rays normal. CAT brain scan (September 1977) showed dilatation of the 4th ventricle and slight enlargment of the pontine cisterns and cisterna magna, the appearances suggesting cerebellar atrophy. Blood (October 1977) Hb 11·8 g/dl, WBC 4·8 × 10^9/l with normal differential, urea 6·6 mmol/l (39·6 mg/100 ml), electrolytes normal. Measles serum complement fixation titre (CFT) 1:16 384; IgM specific for measles 1:12. Serum immunoglobulins: IgG 12·0 g/l, IgA 2·4 g/l, IgM 2·5 g/l. Plasma cortisol at 2200 hours 760 nmol/l (27 µg/100 ml), at 0800 hours 680 nmol/l (25 µg/100 ml). CSF cells normal, protein 0·44 g/l (44 mg/100 ml), IgG 0·108 g/l (10·8 mg/100 ml), measles CFT 1:128. EEG showed a generalised high voltage theta/delta wave activity with periodic higher voltage slow wave complexes, which at times had a notched appearance, occurring every 5–6 seconds; these arose predominantly over the right hemisphere initially but were more symmetrical in a later EEG.

Necropsy

Both legs were severely wasted and there was pronounced kyphoscoliosis. The ileal bladder contained a small amount of clear urine which readily refluxed into dilated ureters and there was bilateral hydronephrosis. Histological studies showed chronic pyelonephritis, centrilobular liver cell necrosis, and bronchopneumonia. Neither local recurrence of neuroblastoma nor metastases was identified. The lower lumbar and sacral regions of the spinal cord were completely atrophic and immediately above this area a 1·5 cm length of the upper lumbar cord was slightly expanded by greyish gliosis. The brain was externally unremarkable but transection after fixation showed slight induration and pinkish grey discoloration of the cerebral white matter, especially in the occipital lobes.

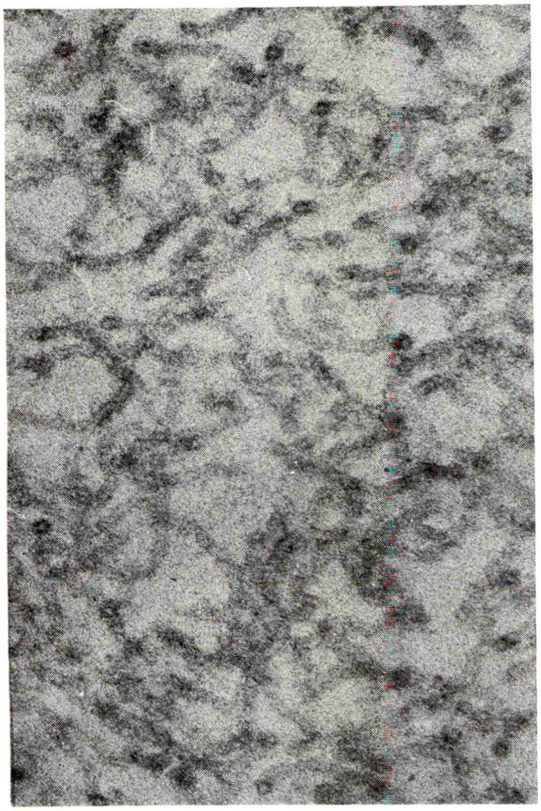

Figure *Electron micrograph showing intranuclear microtubules. × 128 000.*

The histological features of the brain were typical of SSPE with extensive subacute inflammatory changes affecting both grey and white matter. The main characteristics were perivascular cuffing by small mononuclear cells, mainly lymphocytes, depletion of myelinated fibres in white matter accompanied by conspicuous astrocytic gliosis, degeneration and fall-out of neurones, with various degrees of reactive microglial proliferation and frequent intranuclear eosinophilic inclusion bodies mostly in oligodendrocytes. Electron microscopy showed intranuclear tubular structures indistinguishable from paramyxovirus nucleocapsids (Figure).

Discussion

The clinical diagnosis of SSPE in this case was suggested by the history of slowly progressive symptoms with prominence of mental deterioration followed by involuntary movements and myoclonus before there was major loss of cortical function. The EEG with periodic complexes at 5–6 seconds superimposed upon a generalised abnormality supported this.

In contrast, a review of the 20 cases of IME so far reported shows that this condition often starts with unilateral seizures progressing to generalised seizures and hemiplegia; occasionally there may be myoclonic jerks, epilepsia partialis continua, and involuntary movements. The progression from somnolence to coma may be very rapid, with death in several cases as early as 2–8 weeks after onset of symptoms. Except for 3 patients who survived with neurological damage, all have died within 5 months of onset. The EEG usually has a generalised abnormality often with focal discharges.

The CSF in IME is usually normal although there may be a slight increase in protein and cell count. The pronounced increase in IgG in our case is typical of SSPE. High measles antibody titre occurs in serum and CSF in both conditions and the measles virus has now also been isolated from the brain in IME (Aicardi *et al.*, 1977). A high level of measles-specific IgM in the CSF has so far been recorded only in SSPE, and in our patient it was 1:12.

In a comparison of the pathological changes in SSPE and IME, several reports of the latter have drawn attention to a singular lack of perivascular cuffing by inflammatory cells. This has, however, been present in most cases. Inclusion bodies and astrocytic gliosis typical of SSPE are also almost always noted in IME although microglial proliferation is somewhat less constant. Thus there is not a clear histopathological distinction from SSPE and the differences observed may largely depend on the duration of the disease.

SSPE and IME may well represent opposite ends of a spectrum of disease induced by measles virus persisting in the brain, and the nature and severity of immunological deficiency at the time of the initial infection may determine the latent period and rate of progress of the encephalitis. Various immunological abnormalities have been found in patients with SSPE (Addy, 1977) but proof that they were present when primary infection occurred and predisposed to the 'slow' virus infection is lacking. Our patient contracted measles when there were good reasons to suspect that cell-mediated immunity was still depressed: the exanthem appeared 3–4 weeks after cyclophosphamide treatment had been stopped because of neutropenia, and the girl received radiotherapy which has been shown to prolong drug-induced immunosuppression (Campbell *et al.*, 1973). Typical SSPE began 8 years later.

The only similar recorded case was that of Loirat *et al.* (1971); during immunosuppressive treatment for the nephrotic syndrome, this boy developed an exanthema suggestive of measles and he died 2 years later of an SSPE-like illness during which the serum measles antibody rose to a high titre. Necropsy was not performed.

We thank Dr E. McKay for his comments and permission to report details of the patient under his care, and Dr A. W. Downie for advice.

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Response of neonatal hypocalcaemia to 1α-hydroxyvitamin D3

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SUMMARY Administration of 1α-OH-D3 to hypocalcaemic neonates (mean ±SD, serum calcium 1·50 ± 0·13 mmol/l) significantly increased serum calcium in all 24 infants within 48 hours after starting therapy (mean ±SD 1·83 ± 0·23 mmol/l). The time required to correct hypocalcaemia was significantly shorter (2·04 ± 0·56 days) in infants treated with 1α-OH-D3, than in 24 infants treated with calcium gluconate infusions (4·12 ± 1·0 days). Treatment with 1α-OH-D3 was effective, easy to maintain, and produced no side effects.

Decreased parathyroid hormone (PTH) secretion and/or end organ response, increased serum calcitonin concentrations, and defects in vitamin D metabolism have been implicated in the pathogenesis of neonatal hypocalcaemia (Tsang *et al.*, 1976). 1α,25-Dihydroxyvitamin D (1α,25(OH)$_2$D), the biologically active metabolite of vitamin D, which stimulates intestinal calcium transport, is synthesised by successive hydroxylation of vitamin D in the liver and kidney (DeLuca, 1976). Derangements in these metabolic pathways, and maternal vitamin D deficiency during pregnancy, may well be important factors in the pathogenesis of neonatal hypocalcaemia (Hillman and Haddad, 1975; Weisman *et al.*, 1976; Hillman *et al.*, 1977). We, therefore, investigated the effect of 1α-hydroxyvitamin D3 (1α-OH-D3), a readily synthesised and commercially available analogue of 1α,25(OH)$_2$D$_3$, in the treatment of neonatal hypocalcaemia.

Patients and methods

48 infants (mean gestational age 33·5 ± 2·8, ±SD

weeks; mean weight 1947 ± 613g, ±SD) with symptomatic hypocalcaemia presenting within the first 4 days of life were studied, with the informed consent of the parents. Most infants had muscular twitchings or apnoeic episodes and a few had frank convulsions. The serum calcium of each infant averaged <1·75 mmol/l (7 mg/100 ml). The radioassayable serum 25-hydroxyvitamin D concentrations were >25·0 nmol/l (≃10 ng/ml) in all patients (mean ±SD 58·0 ± 22·9 nmol/l (23·2 ± 9·1 ng/ml). All the patients received brief IV infusions of calcium gluconate to alleviate symptoms and were then divided randomly into two groups equally matched in gestational age and 1-minute Apgar score. Group 1 received 1α-OH-D3, 0·33 μg in arachis oil orally, twice daily for 5 days. Group 2 received IV infusions of calcium, 20 mg/kg per day, as 10% calcium gluconate. Serum calcium was determined twice daily by Eppendorf flame photometer.

Results

Administration of 1α-OH-D3 significantly increased serum calcium in each patient within 48 hours after starting treatment (Table) and there was no recurrence of the symptoms of hypocalcaemia. The mean recovery time (time required to correct hypocalcaemia) was significantly ($P<0·01$, *t* test) shorter in infants treated with 1α-OH-D3 (group 1) than in infants treated with calcium gluconate infusions (group 2). No episodes of hypercalcaemia were recorded. All infants remained normocalcaemic when 1α-OH-D3 was stopped.

Table *Data for hypocalcaemic infants before and after treatment*

Group	*Treatment*	*Calcium mmol/l (mean ±SD)*		*Calcium >1·75 mmol/l*
		Before treatment	*48 hours after treatment*	*Mean (±SD) recovery time (days)*
1	1α-OH-D3	1·50 ± 0·13	1·83 ± 0·23*	2·04 ± 0·56**
2	Calcium gluconate	1·54 ± 0·10	1·56 ± 0·28	4·12 ± 1·00

*Significantly different from group 2, $P<0·05$; **significantly different from group 2, $P<0·01$.
Conversion SI to traditional units: Calcium—1 mmol/l ≈ 4 mg/100 ml.

Discussion

Renal 25-hydroxyvitamin D-1α hydroxylase activity is influenced by a variety of factors including serum and tissue concentrations of calcium, PTH, 25(OH)D, and $1\alpha,25(OH)_2D$ (DeLuca, 1976). Thus, impairment in the synthesis of $1\alpha,25(OH)_2D$ may be the end result of the derangements in PTH, calcitonin, and vitamin D metabolism, which have been implicated in the pathogenesis of neonatal hypocalcaemia (Tsang *et al.*, 1976; Weisman *et al.*, 1976). Indeed, newborn rats are unable to synthesise 1α,25(OH)D3 to detectable levels (Weisman *et al.*, 1976). The present data demonstrate the effectiveness of 1α-OH-D3 in the treatment of neonatal hypocalcaemia and are in good agreement with those of earlier studies in which $1\alpha,25(OH)_2D_3$ was evaluated for the prevention (Chan *et al.*, 1978), and treatment (Kooh *et al.*, 1976), of neonatal hypocalcaemia, and with one case report in which 1α-OH-D3 was given to an infant with protracted hypocalcaemia (Doxiadis and Lapatsanis, 1977).

1α-OH-D3 is converted to $1\alpha,25(OH)_2D_3$ *in vivo*, a necessary step for its biological activity (DeLuca, 1976). It was suggested that the hydroxylation of vitamin D to 25-hydroxyvitamin D may be impaired in premature infants (Hillman and Haddad, 1975). In our study, however, premature infants responded to treatment with 1α-OH-D3, indicating that 25-hydroxylation of 1α-OH-D3 had taken place in these infants. Traditional treatment of neonatal hypocalcaemia with continuous calcium gluconate infusions is difficult to maintain and may cause severe complications (Tsang *et al.*, 1976). However, 1α-OH-D3 treatment was easy to maintain and produced no side effects.

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Acute intermittent porphyria and epilepsy

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SUMMARY A 14-year-old boy had suffered from intermittent acute hepatic porphyria, myoclonic convulsions, and mental retardation (Lennox-Gastaut syndrome). The porphyria was treated by stopping the administration of phenobarbitone and phenytoin. Sodium valproate at a dose of 70 mg/kg per day lessened the severity and frequency of convulsive crises.

Acute intermittent porphyria (AIP) is rare in children, but is not unknown. In a survey of reports on such children, Barclay (1974) found 37 cases but these were not all fully documented. In our opinion the age of the patient is of particular interest as is the association of AIP with epilepsy. The only 4 cases of hepatic metabolic disorder of porphyrins to have been fully described in infants associated with epilepsy are 3 of hereditary coproporphyria (Birchfield and Cowger, 1966; Haeger-Aronsen *et al.*, 1968; Houston *et al.*, 1977) and one of hepatic porphyria not better identified (Houston *et al.*, 1977).

Case report

A 14-year-old boy (born 4.12.1963) was the second child in an otherwise apparently healthy family with two other children. However, when examined his 39-year-old mother was found to have latent AIP.

During early infancy our patient had been moderately retarded in his psychomotor development, especially walking and speech. At 3 years he had generalised convulsions; during the clonic phase these mainly affected the right side. He was put on a course of phenobarbitone and phenytoin, or one of these, and although this treatment was changed and reassessed periodically, his condition did not improve. The length and frequency of the attacks increased and there was concurrent and progressive slowing down of his psychomotor development and learning ability, until at age 5, his IQ was 75. Because of his mental retardation and the fact that his repeated convulsive crises did not respond to drugs, he was sent to an institution and by age 11 his IQ was at a 5-year level.

Before coming to our attention, this child had three times been admitted to surgical departments with acute abdominal symptoms and constipation.

At age 13 he was admitted to a medical department with bronchopneumonia and underwent haemodialysis for anuria. Then, for the first time, in addition to the generalised convulsions, petit mal crises of variable length were recorded. The first was noted on the 14th day after admission. From the EEG findings, the neuropsychiatrist interpreted the neurological symptoms as Lennox-Gastaut syndrome. When the anuria ceased, despite the fact that the boy's urine was dark brown, no further diagnosis of AIP was registered.

We first saw this child in 1977 when he was aged 14. He had been admitted for clinical observation because of renewed episodes of abdominal pains and constipation. At that time there was a clinical picture of an acute attack of AIP.

We stopped those drugs which are now known to provoke acute crises of AIP and were able to reduce the number of seizures and ameliorate the acute clinical symptoms. By giving him sodium valproate *alone* (70 mg/kg per day) we have been able to reduce the frequency, duration, and gravity of the fits. With this diminution of fits and, subsequently, almost complete elimination of such crises, the patient's mental condition has improved.

Table 1 *Urinary porphyrins and precursors and uroporphyrinogen–1–synthetase enzyme activities in erythrocytes*

	Urinary porphyrins and precursors				*Uroporphyrinogen–1–synthetase enzyme activities in erythrocytes*		
	Age (*years*)	*Date*	*ALA* (*mg/24h*)	*PBG* (*µg/24h*)	*URO* (*µg/24h*)	*COPRO* (*µg/24h*)	*pmol/mg URO per mg protein per hour*
Propositus	14	11/1/78	52·5	114	6885	18450	140
Mother	38	11/1/78	12·8	15·52	968	1592	94

ALA = δ-Aminolaevulinic acid normal less than 3·5 mg/24h. PBG = porphobilinogen normal 0µg/24h. URO = uroporphyrins normal 0–30 µg/24h. COPRO = coproporphirins normal: male 130–248 µg/24h. female 92–176 µg/24h. Uroporphyrinogen-1-synthetase enzyme activities in erythrocytes, normal 220–380 pmol/mg URO per mg protein per hour.

Table 2 *Seizure types and EEG patterns in our patient and in reports of 3 other children with hepatic symptomatic porphyria*

Case	*Year*	*Age at onset (years)*	*Type of porphyria*	*Seizure types*	*EEG*	*No. of antiepileptic drugs used*	*Mental state*
Present	1979	3	Acute intermittent porphyria	Falls, myoclonic tonic, clonic, atypical absences, hemiconvulsions, absence status	Slow spike wave	3	Severe mental handicap at age 14
Houston *et al.*	1977	2½	Hereditary coproporphyria	Falls, myoclonic tonic, atypical absences, clonic and hemiconvulsions	Slow spike wave, fast spiking in seizures	14	Hyperkinetic severe mental handicap at age 10
Haeger-Aronsen *et al.*	1968	10	Hereditary coproporphyria	Tonic, clonic with left clonic	'Partially paroxysmal'	1	Normal at age 13
Birchfield and Cowger	1966	3½	Hereditary coproporphyria	Febrile grand mal, 'akinetic', myoclonic, 'minor motor', atypical absences	Spike and wave repetitive spikes in seizure	14	Dullish normal at age 7

Discussion

The following points are of interest. (1) The mental handicap in our patient was the same as that described in 3 of 5 other cases (Birchfield and Cowger, 1966; Houston *et al.*, 1977). (2) There is a continuous need to adjust the treatment. (3) The severity of the epilepsy was such that the paroxysmal activity was 2·5 Hz on the EEG, suggesting a seizure disorder such as the Lennox-Gastaut syndrome. The epilepsy was equal in severity to the other cases (Birchfield and Cowger, 1966; Houston *et al.*, 1977). (4) The symptoms became much less when barbiturates and phenytoin were stopped and sodium valproate given alone at a dose of 70 mg/kg per day.

We, therefore, believe that our case lends further support to the claim of Houston *et al.* (1977) that there is a correlation between epilepsy and acute porphyria. In fact, the failure to diagnose AIP early and the unsuccessful anticonvulsive therapy probably hastened the acute crises which were attributed to AIP only in retrospect.

Table 1 gives the amounts of urinary porphyrins and precursors and uroporphyrinogen-1-synthetase enzyme activities in erythrocytes found both in the patient and in the mother on which the diagnosis is based (using the method of Grandchamp *et al.*, 1976).

Table 2 gives the principal clinical findings in our patient and those previously reported.

We thank Professor E. Rocchi, Department of Therapeutic Medicine, Institute of Medical Clinics, Modena University, Italy, for carrying out the enzymatic erythrocite assays and the quantitative evaluations of urinary porphyria.

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Munchausen syndrome by proxy in twins

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SUMMARY A family is described in which twin infants had repeated admissions for apparent haemoptysis. It was proved that the mother was simulating these episodes and she eventually injured one of the children with a pin. The mother has subsequently shown some evidence of a Munchausen tendency in herself.

The spectrum of child abuse is ever widening with the recognition of the more obscure types of injury. Meadow (1977) described a child whose symptoms were fabricated by her mother, causing numerous investigations. He called this Munchausen syndrome by proxy. A further family is described in which there were similar occurrences.

Case report

Twins, a boy and a girl, weighing 2·5 kg and 1·9 kg respectively were born at 36 weeks' gestation by spontaneous vertex delivery. There were no immediate problems at birth. The boy was allowed home with his mother after 5 days. The girl was kept in the special care nursery for 3 weeks during which time parental visiting, although encouraged, was infrequent.

Both parents, previously married, were known to the Social Services Department because each had had children who were suspected, but not proved, to have been nonaccidentally injured. These children are now in the custody of the other remarried partners.

During the first 4 months, despite intensive support, there were 5 admissions for relatively minor illnesses. Then, on consecutive evenings, both twins were admitted with a history of having vomited blood. No cause was found for this and they were subsequently discharged. The same evening the girl was readmitted and the boy the next night, again having vomited blood. On this occasion, blood-stained bibs were produced. Aspiration of stomach contents showed no evidence of blood and again no cause was found for the bleeding. The next day, while the mother was feeding the boy in hospital, she reported that he was again bleeding. Blood was present on his clothing and on the mother's nursing gown. Thorough examination showed no bleeding points on the child. Mother and baby were known to have different blood groups so the clothing was sent for forensic analysis. At this stage it was thought that the mother was probably simulating the bleeding by injuring herself, and this was confirmed at a much later date by the forensic tests. However, the twins were allowed home in the knowledge that the mother had 'an escape route' when under pressure. The next evening both twins were readmitted, again having vomited blood and no cause was found.

A few days later while the mother was momentarily alone with the twins, blood appeared on the girl's chin. A nurse heard the baby crying, immediately examined her, and found a small bleeding point on her lower lip. He also saw a nappy pin that was almost hidden in the mother's hand. The twins were wearing selfadhesive disposable nappies which did not require the use of pins. The mother subsequently admitted injuring her child with the pin, was charged with assault, and found guilty. She consistently denied falsifying any of the previous episodes. The children were then both placed in the care of the local authority.

Discussion

Although it was recognised from before birth that the twins were at risk of child abuse they appeared to thrive and develop normally. The repeated admissions were accepted as a means of helping the family, although during admissions the parents rarely visited, and there was always delay in discharging the twins. In retrospect, we suspect that the mother felt unable to cope with both twins from early in their life, but could not admit this to her cohabitee. She found a means of escape by injuring herself and gaining relief from the children without showing her inadequacy. We think she may have deceived her entire family as several members had been present in the room on occasions when the bleeding had occurred. Why she should eventually injure one of the children is open to speculation, particularly as she had no concept of different blood groups and was therefore unaware that her falsification could be proved.

This case report differs from those previously described in that the sole gain to the mother was of relief from the children. The mother showed no previous Munchausen tendency, but since the twins have been taken into care she has presented to her doctor with a history of haemoptysis and also with a bleeding lesion on her breast which was extremely slow to heal.

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Change of reference style

From January 1980, the *Archives* will change its style for citing references and will follow the number system. We are making this change in order to conform with the 'Vancouver style' of uniform requirements for manuscripts submitted to biomedical journals.

Previously the *Archives* has used the Harvard reference system. Its advantages and disadvantages compared with those of the number system have seemed evenly balanced, but the editors have been aware of the burden imposed on authors and their secretaries by the different styles which different journals require. Therefore, with the unanimous agreement of the editorial committee, we have decided to support a move whereby a large—and increasing—number of major medical journals will accept manuscripts presented in one agreed style.

The system numbers references consecutively in the order in which they are first mentioned in the text. References are identified in the text by arabic numerals. For further details see instructions to authors inside the front cover, and the references cited.[1,2]

From now onwards all manuscripts submitted should accord with the new style.

[1] International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979; **1**: 533–535.

[2] Lancet. The Vancouver style. Uniform requirements for manuscripts submitted to biomedical journals. *Lancet* 1979; **1**: 429–430.

Archives of Disease in Childhood, 1979, **54**, 648–651

Correspondence

Anaemia in childhood coeliac disease

Sir,

There is considerable variation in the reported incidence of anaemia in childhood coeliac disease (Hamilton *et al.*, 1969; Walker-Smith, 1975). Both iron and folic acid deficiency may be present, but how often is not certain, and the value of red cell folate as a screening test is controversial. With these problems in mind, we examined the records of 91 children aged 2 months to 9 years, who had coeliac disease confirmed by jejunal biopsy over a 10-year period (1966–76) at the Bristol Children's Hospital.

The Figure shows the haemoglobin levels of children with coeliac disease and indicates which of these children had normal and which had low red cell folate levels (normal range of haemoglobin, Lascari, 1973). 37% of children were anaemic at diagnosis. The incidence of anaemia will depend on the population and the definition of anaemia. The incidence varies from 19% (Walker-Smith, 1975) to 80% (Hamilton *et al.*, 1969). Our results show that the incidence of anaemia is affected by the age distribution of the children at diagnosis. Mean haemoglobin was lower, and incidence of anaemia much greater (16/23 compared with 18/68, $P = <0\cdot05$) in children of at least 2 years. The reason for this difference with age is not clear. The duration of the illness before diagnosis may be important because of the time needed to deplete body stores of iron before erythropoiesis is effected. The mean duration of symptoms was much longer (184·4 weeks compared with 16 weeks) in the older children.

Coeliac children, whether they are anaemic or not, are likely to have low serum iron levels at the time of diagnosis. 87% (40/46) serum iron estimations were <12 µmol/l (<67 µg/100 ml), and percentage saturation of transferrin was below 16% in 93% of estimations. Blood film examinations showed that all anaemic children had moderate or pronounced red cell hypochromia. There was little morphological evidence of megaloblastic change. Three older children, all with low red cell folate levels, had some macrocytic red cells but hypersegmented neutrophils were not seen. Half (9/18) of red cell folate estimations in anaemic children were normal. Red cell folate is a poor screening test for childhood coeliac disease because half (17/34) of the estimations were normal in coeliac children at diagnosis.

We thank Dr Mary Seacome for her help.

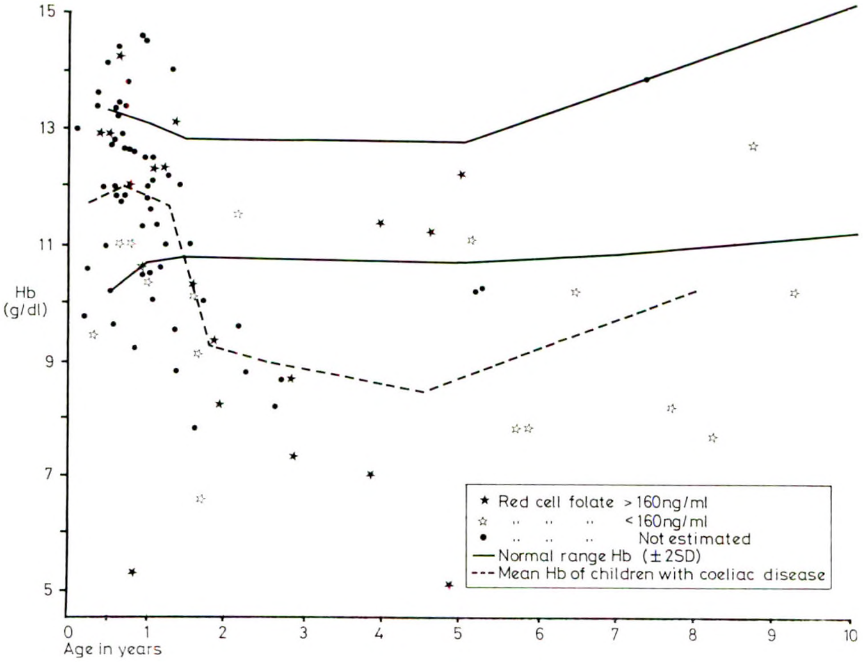

Figure *Haemoglobin levels in 91 children with coeliac disease.*

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Coxsackievirus type A16 infection in a neonate

Sir,

Coxsackievirus type A16, commonly associated with the characteristic syndrome of hand, foot, and mouth disease, is an unusual infective agent in children under one year of age, particularly in the neonatal period. A short nonspecific illness in a newborn baby was shown to be associated with hand, foot, and mouth disease in his mother, and Coxsackievirus type A16 was recovered from both.

Case report

A 3-week-old baby boy was admitted with a 24-hour history of drowsiness and refusing feeds. Delivery had been normal at 35 weeks' gestation after premature rupture of membranes and intermittent labour pains for 10 days. Birthweight was 2·7 kg, and the baby had been nursed in the special care unit for 10 days because of a feeding problem associated with mild jaundice. Breast feeding had been maintained.

He was a well nourished but drowsy and slightly jaundiced infant: temperature 34·6°C; Dextrostix 25mg/100 ml. A full infection screen failed to show any focus of infection, and a provisional diagnosis of cold injury was made. It was found that his mother had been ill for 4 days previously, with a febrile 'flu-like' illness, associated with painful ulceration of her mouth, feet, and hands, Coincidentally with the infant's illness, a sibling also had nonspecific malaise.

Coxsackievirus type A16 was grown in monkey-kidney tissue cultures from maternal throat swab and vesicle fluid, and from the infant's throat swab; the infant's CSF was acellular and sterile.

The infant initially required tube feeding, and was nursed in an incubator until his temperature rose to normal. He was discharged home clinically well 5 days later.

Coxsackievirus type A16 infections are most commonly associated with hand, foot, and mouth disease, but have also been found in encephalitis, meningitis, myocarditis, and pericarditis. The highest incidence is in the 1- to 3-year-old age group (Gamble, 1962), and the incubation period is short, between 3 and 6 days. The disease is highly contagious, primary cases occurring in children, and spreading horizontally from sibling to sibling, and to parent.

The present case is interesting with regard to the age of the patient and the symptoms, which were relatively mild and atypical. Previously, neonatal infection with this agent has been reported in association with fatal myocarditis (Wright *et al.*, 1963; Golgberg and McAdam, 1965), but neonatal infections are rare, probably because of protection by maternal antibody (Gear, 1958; D. R. Gamble, 1977, personal communication). There are no previous reports of this infection being acquired postnatally from the mother. In this instance breast milk was not examined virologically, which might have shown the route of transmission.

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Bronchodilator drugs and young children

Sir,

In their paper (*Archives*, 1978, **53,** 532), Lenney and Milner concluded that wheezy children under age 18 months did not respond to treatment with nebulised salbutamol, as measured by respiratory resistance or thoracic gas volume. They also quoted two other studies (Radford, 1975; Rutter *et al.*, 1975) which had similar conclusions. All these studies were performed in the recovery stage of an acute attack. In my experience, at the height of an attack, in the most severe stage, two-thirds of infants under one year show improvement in auscultatory findings when treated with nebulised salbutamol or isoetharine (König, 1978). Although no pulmonary function tests were done on infants of this age, there was a significant reduction in respiratory rate and dyspnoea score.

Although there is little doubt that the response of young infants to bronchodilators is less good than that of older children, I think that in the acute stage a substantial number of them do benefit and it is worth a trial.

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Dr Milner and co-workers comment:

We were interested to hear of Dr König's experience with nebulised salbutamol in children under one year. We accept that all our studies were carried out during the recovery phase but we have not found that any child under one year has obtained any useful, clinical benefit from nebulised salbutamol when administered in the acute phase. Since our paper was published, two children between the ages of 12 and 18 months have responded well, and we have since heard of another who apparently obtained benefit by age 11 months. We still recommend that salbutamol be given to all wheezing children over one year but think it unlikely that many children younger that this will respond to this form of treatment.

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Intrathecal ATS and high dosage diazepam in neonatal tetanus

Sir,

We should like to make a few comments about the report by Khoo *et al.* (*Archives*, 1978, **53**, 737). Seven of the 19 neonates studied required total paralysis with IPPV for uncontrolled spasms, 2 died, and 5 more might have died but for total paralysis and IPPV. Therefore, it is not justified to say that improved survival was due to administration of high doses of diazepam alone.

Recently we initiated a study on the efficacy of a regimen consisting of intrathecal administration of antitetanus serum (ATS), and high doses of diazepam (15–30 mg/kg per day) and chlorpromazine (15–30 mg/kg per day) intravenously.

Between July and October 1978, we studied 10 neonates (Table). Diagnosis was on clinical grounds, and severity was graded using the criteria of Patel and Joag (1959). Immediately after admission an IV line was established and diazepam administered at the rate of 1 mg/kg per minute until the infant was free of spasm and rigidity. This was followed by administration of ATS, 250 IU intrathecally, and 1500 IU IV. Penicillin and gentamicin (5 mg/kg per day) were given. Infants were nursed in the paediatric ward. The umbilical cord was cleaned with spirit, and painted with gentian violet routinely. Pharyngeal suction was done at regular intervals.

Subsequent muscle relaxation was achieved by alternate IV administration of 2·5–7·5 mg diazepam and chlorpromazine, each at 2–4 hourly intervals (total daily dose of each drug 15–30 mg/kg). Once spasms had been controlled, a nasogastric tube was inserted for feeding and giving diazepam and chlorpromazine. Sedation was gradually tapered off at a rate of 10–15% of total dose administered at intervals of 1–2 days, depending on the degree of hypertonia. None of the infants was given IPPV with total paralysis.

Eight neonates recovered completely and 2 died, one of fulminant bronchopneumonia and the other with aspirant pneumonia. The average duration in hospital for the survivors was 20 days, and the average period for IV diazepam and chlorpromazine 3·4 days. We observed that the shorter the interval between the onset of the tetanus neonatorum and the intrathecal ATS, the quicker

Table *The 10 neonates* studied*

Case	*Gestational weight (kg)*	*Age at onset (days)*	*Instrument for cord cutting*	*Grade*	*Spasm controlled (hours)*	*Duration of sedation (days)*	*Hospital (days)*	*Outcome*
1	2·8	6	Blade	V	48	20	30	Recovered
2	2·6	6	Blade	V	48	7	13	Recovered
3	2·7	5	Razor	V	9 days	25	25	Recovered
4	3·0	9	Scissors	IV	24	12	12	Recovered
5	2·0 36 weeks	5	Scissors	V	Not controlled	—	—	Died 50 hours after being admitted
6	2·4	7	—	V	36	9	10	Recovered
7	2·1	6	Kitchen knife	V	Not controlled	—	—	Died
8	2·8	7	—	V	72	19	20	Recovered
9	3·0	7	—	V	48	10	11	Recovered
10	2·7	6	Blade	V	120	30	40	Recovered

*All were term except for Cases 5 and 6.

was the control of spasm and the shorter the duration in hospital. Besides thrombophlebitis at the site of venepunctures (probably secondary to benzoic acid present in injectable diazepam) a common complication was apnoea, which responded to partial withdrawal of diazepam. At 3–4 months all 6 neonates who returned for follow-up were developmentally normal.

We feel a combination of high doses of diazepam and chlorpromazine with intrathecal ATS (given early after onset of tetanus) is effective in reducing mortality.

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Dr Khoo and co-workers comment:

We did not claim that the low mortality rate in our patients with neonatal tetanus was due to high dose diazepam alone. Other equally important therapeutic measures that contributed to the improved survival rate in our patients included good nursing care, tetanus antitoxins, antibiotics, nutritional support, and the judicious use of sedatives. In our study, the use of continuous high dose IV diazepam (20–40 mg/kg per day) certainly decreased the mortality rate and also the need for artificial ventilation from 77 to 37% (Khoo *et al.*, 1978).

The treatment regimen advocated by Singhi and Singhi is very similar to ours except for the use of intrathecal ATS and the very high dose of chlorpromazine. The role of intrathecal ATS in the management of neonatal tetanus is still controversial (Laurence, 1975). The reason for injecting ATS into the CSF is to neutralise the tetanus toxin that has penetrated the CNS but has not yet begun to act. Besides, ATS given via the IV route penetrates the blood/CNS barrier poorly, and the levels of antitoxin in the CSF are approximately 400 times less than in the blood (Patel *et al.*, 1963; Ildirim *et al.*, 1969). In 1917, Sherrington obtained good results from the use of intrathecal ATS in monkeys with tetanus. It was subsequently tried in man but eventually abandoned because of adverse reactions to the CNS and doubts about its efficacy (Dietrich, 1940; Pratt, 1945). However, recent reports of the use of intrathecal ATS in tetanus are encouraging (Ildirim, 1970; Sanders *et al.*, 1977; Salimpour, 1978). Ildirim (1970) treated 28 cases of neonatal tetanus with intrathecal ATS and prednisolone mixture and had a low mortality rate of 10·7%. In another clinical trial on 322 cases of adult-type tetanus, 200 units intrathecal ATS (horse) was found to be an effective adjuvant in reducing the mortality rate from 14·5 to 4·5% (Sanders *et al.*, 1977). No complication was encountered apart from occasional difficulty in giving ATS intrathecally, while remarkable relaxation was observed in the patients.

With the availability of human antitetanus serum, which is relatively free of allergic side effects and less irritating to the CNS, the prospects for intrathecal ATS (human) is promising, but needs further tests before it can be recommended.

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Archives of Disease in Childhood, 1979, **54**, 652

Book reviews

Down's Syndrome. The Psychology of Mongolism. By David Gibson. (Pp. 366; illustrated + tables. £18.50, hardback.) Cambridge University Press: Cambridge. 1979.

This book is a superb review of past and present literature on Down's syndrome from both sides of the Atlantic. Each aspect of psychological development has its own chapter with evaluation at the end. A more concise summary of some chapters would have been helpful. The chapters on foundation of intelligence and language are particularly good. Important medical aspects which contribute to the psychological profile are given due prominence—for example, intermittent hearing loss and disproportionate delay of language development—treatment with thyroxine having no effect in those who are euthyroid.

Remediation programmes are discussed and the short-term gains compared with the few long-term results.

This book is strongly recommended to anybody who is interested in Down's syndrome.

GILLIAN BAIRD

Pediatric Bronchology. By Edgár Székely and Edit Farkas. (Pp. 628; illustrated + tables. £39.50, hardback.) University Park Press: Baltimore. 1979.

This massive book is based on the authors' experience and expertise in over 30 000 bronchoscopical and radiological examinations of the bronchial tree during a period of 20 years at the Public Children's Sanatorium, Budapest. By its very nature, therefore, this volume is authoritative and is a highly significant contribution to our knowledge in this field. The contents of the book are divided into three sections: a general introduction to the concepts of paediatric bronchology, a detailed discussion of congenital abnormalities and pathological entities affecting the bronchi, and an account of the contribution made by bronchial catheterisation. The chapters are well illustrated with good quality colour endobronchial photographs and well reproduced contrast bronchograms. There is an extensive bibliography and indexes to authors and subjects.

Paediatric bronchology is a highly specialised field and there can be few institutions that could rival the experience of the authors. This work therefore will be of the greatest interest to all those in this branch of paediatrics. It should be eagerly read and used as a book of reference by paediatricians interested in pulmonary diseases, and by all those in allied specialities involved with examination of the bronchial tree in infants and children. Undoubtedly paediatric radiologists will find much new information to assist their evaluation of bronchographical examinations.

The book is beautifully produced and bound. The scope of the contents reflects the interests of the authors so that the reader must not expect all tracheobronchial diseases to be covered. For example, burns of the tracheobronchial tract, an increasingly common occurrence in this country, are not mentioned. It is unfortunate that the English translation does not match the other qualities of the production. The text therefore is not uniformly clear and it is to be hoped that this will be improved in the next edition. The references are mainly to European Continental literature which poses considerable problems to the English reader if original articles are to be consulted.

GORDON H. BUSH

Surgery of the Neonate. By Arnold G. Coran, Douglas M. Behrendt, William H. Weintraube, and Denis C. Lee. (Pp. 272; illustrated + tables. $32.50, hardback.) Little, Brown: Boston. 1978.

This volume, in the very specialised field of surgery in children in early infancy, details the techniques used by a group paediatric surgeons in Ann Arb Michigan.

The text is clear, well produced, easy follow, and reasonably succinct. There a brief list of references, some *x*-ı plates, and black and white line drawin Most of the drawings are clear and w produced, but the quality of the rad graphs leaves much to be desired. T abdominal *x*-rays are adequate, but found the reproductions of the ch *x*-rays and cardiac angiograms disappoi ing and of little value.

Descriptions of individual diseases a forms of treatment are reasonably cle but inevitably in this type of book t amount of text does not allow detail discussion of the results of treatment, n does it give alternative approaches.

I do not think this book will have wide appeal in this country. The work the neonatal surgeon in general no long includes special areas—such as cardi surgery, this falling within the province the specialised departments.

I feel the book is too specialised for t general registrar in training, and ina equate for the specialist who will seek more comprehensive presentation and d cussion of alternative techniques a results.

P. B. DEVERA

Shorter notice

Aplastic Anaemia. Edited by C. G. Gear (Pp. 249; illustrated + tables. £12.5 hardback.) Bailliére Tindall. 1979.

Comprehensive coverage of a fashionab and fascinating topic. Strong on clinic features and the limited treatment ava able, but I should have liked more abo the pathophysiology of marrow failur A useful chapter about marrow failure childhood with comprehensive referenc up to 1978. Otherwise a book for t specialist and/or the enthusiast.

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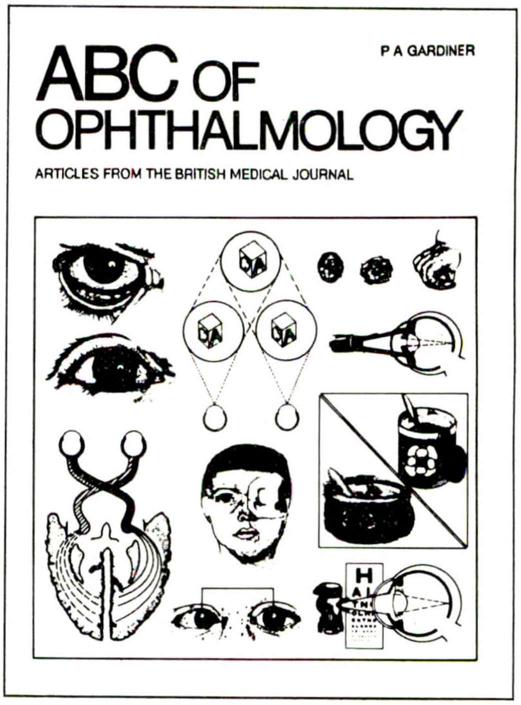

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PEDIATRIC RESEARCH

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A. K. Tanswell and B. T. Smith (Kingston, Ontario, Canada)

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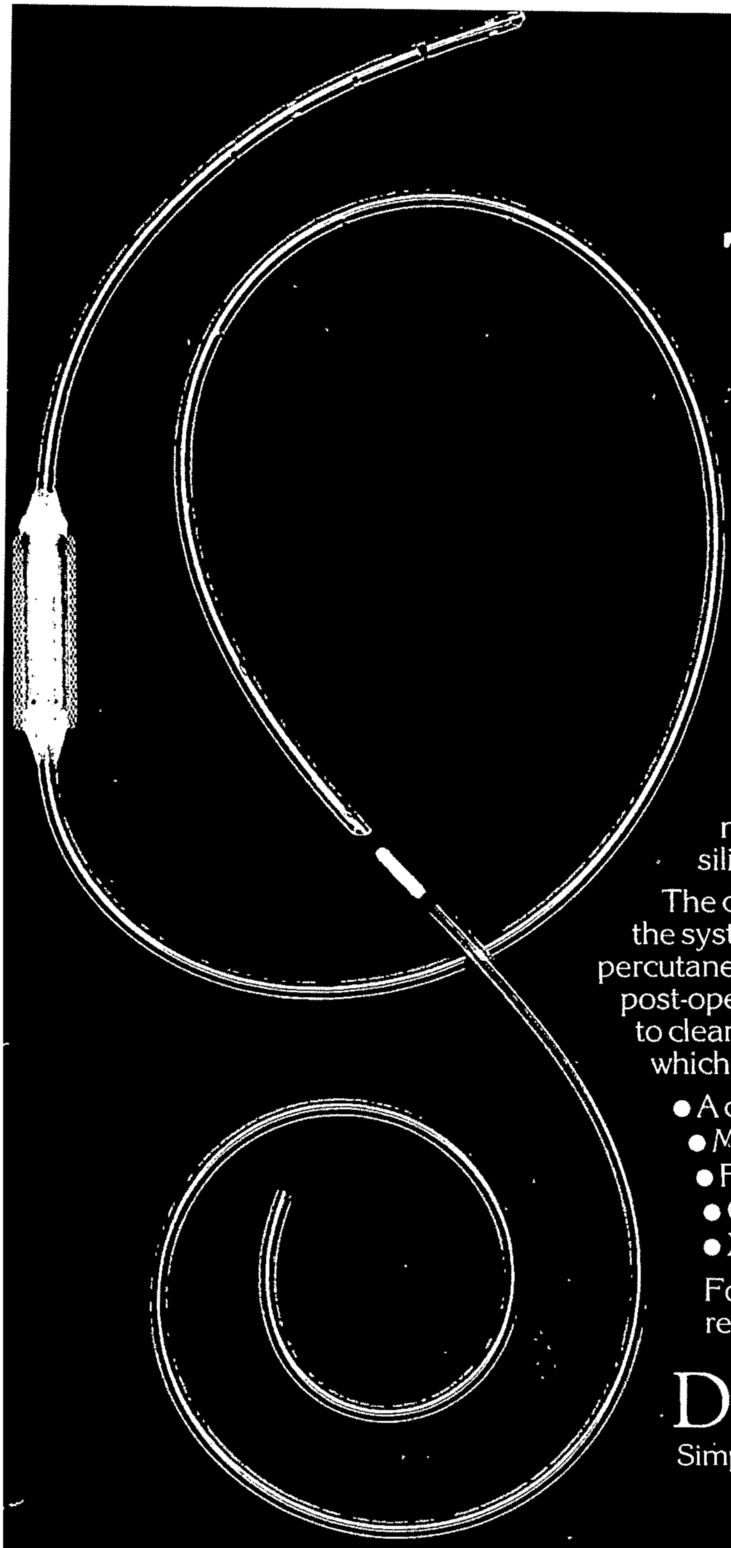

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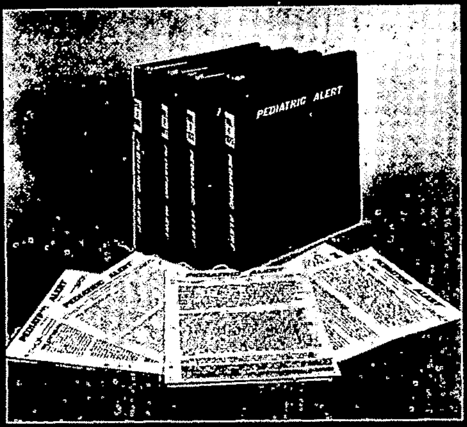

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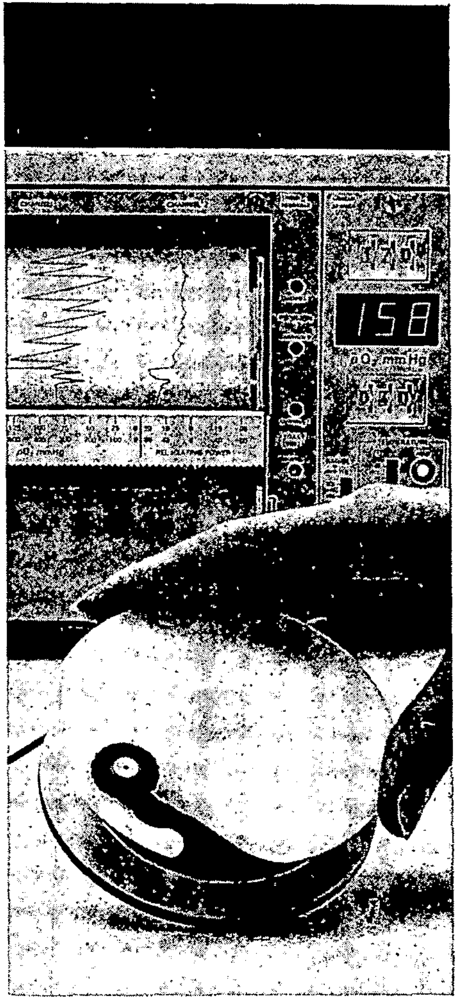

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Total parenteral nutrition in very low birthweight infants: a controlled trial

V. Y. H. YU, B. JAMES, P. HENDRY, AND R. A. MACMAHON

Department of Paediatrics, Queen Victoria Medical Centre, Melbourne, Australia

SUMMARY 34 preterm infants with birthweights <1200 g were randomly assigned to total parenteral nutrition (TPN) or oral (Milk) feeding regimens for the first 2 weeks after birth. Infants in the TPN group were started on a modified Vamin-based glucose amino-acid infusion and Intralipid. The daily amounts of carbohydrate, amino-acids, and fat infusions were increased. In the Milk group, infants were started on intermittent gavage feeding, supplemented with a glucose-electrolyte infusion as necessary. The overall mortality rate did not differ in the two groups. Four infants in the Milk group developed necrotising enterocolitis but none did in the TPN group. Despite mean daily energy intakes which were not greatly different, there were much higher mean daily intakes of carbohydrate and protein in the TPN group compared with the Milk group. Fat intake in the TPN group was lower than in the Milk group in the 1st week because of neonatal jaundice which contraindicated the use of Intralipid. There was no difference in the mean daily fat intake by the 2nd week. Although mean daily weight loss in the 1st week and the maximum postnatal weight loss in the two groups were similar, infants in the TPN group had a greater mean daily weight gain in the 2nd week and took less time to regain and maintain birthweight. Metabolic complications were equally common in both groups and were reversible with early recognition. Limits of tolerance for water and most nutrients tended to be variable and the nutritional programme had to be adjusted for each baby. Nevertheless, we found that TPN, when properly managed, is an effective and safe procedure in very low birthweight infants.

Advances in neonatal intensive care have resulted in better survival of very low birthweight infants. Adequate nutrition in the preterm neonate is considered to be important for immediate survival (Heird *et al.*, 1972b) and for subsequent normal growth and development (Dobbing, 1974). This need for nutritional support often leads to the overzealous early introduction and excessive increases in volume of milk feeding, with a resulting increased risk of aspiration pneumonia (Wharton and Bower, 1965), cardiorespiratory disturbances (Yu, 1976), or necrotising enterocolitis (Yu *et al.*, 1977).

Partial parenteral nutrition as a supplement to inadequate oral intake has been used successfully in low birthweight infants (Benda and Babson, 1971; Cashore *et al.*, 1975), although comparative studies of parenteral supplementation versus conventional feeding regimens showed similar morbidity and mortality (Bryan *et al.*, 1973; Pildes *et al.*, 1973; Brans *et al.*, 1974; Abitbol *et al.*, 1975). The feasibility of supplying complete requirements with total parenteral nutrition (TPN) via centrally placed catheters has been reported (Driscoll *et al.*, 1972; Peden and Karpel, 1972; MacMahon *et al.*, 1975; Hall and Rhodes, 1976; Meng *et al.*, 1977). Although most reports claimed benefits with these techniques all but one (Gunn *et al.*, 1978) lacked proper controls.

Because complications from intragastric milk feeding will contribute to the morbidity and mortality of very low birthweight infants, a study was accordingly designed to compare TPN with intragastric milk feeding supplemented as necessary with only a glucose-electrolyte solution.

Patients

Infants <1200 g birthweights born, at the Queen Victoria Medical Centre or referred within 24 hours

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of birth, were considered for the study. After obtaining informed parental consent, the infants were assigned to a feeding regimen of either TPN or intragastric milk feeding (Milk). Assignment was by random card selection on alternate infants with the infant immediately following qualifying for the opposite study group. 40 infants <1200 g birthweights, admitted to the neonatal intensive care unit during the 12-month period between July 1977 and June 1978, were consecutively enrolled in the study with all babies complying. Six infants died within 24 hours after birth before starting TPN or Milk feeding and were excluded. Therefore, 34 infants were studied.

Methods

Milk group. Intermittent gavage feeding via an orogastric tube was started as soon after birth as the clinical condition of the baby allowed. This was usually begun on day 1 and given every hour using fresh expressed breast milk from the infant's own mother, or a 67 kcal (280 kJ)/100 ml milk formula (Similac, Ross Laboratories, N.S.W., Australia) if the former was unavailable.* The volume of milk was increased as rapidly as tolerated without abdominal distension, gastric retention, or regurgitation. An intake of 150 ml/kg per 24 hours was usually provided but this varied between 100 and 200 ml/kg, depending on the clinical condition of the infant. An infusion of dextrose, water, and electrolytes was supplemented as necessary to maintain normal hydration and biochemical status. The infusate consisted of 5% dextrose and this was increased to a 10% solution as tolerated. As the oral intake increased, so was the infusion rate decreased. Daily oral multivitamin supplements were given from the 1st week. Any infant in the Milk group who remained nil-orally for more than 3 days after birth or in whom feeds had to be withheld for more than 24 hours subsequently during the 2-week trial period was considered as a trial failure and withdrawn. The subsequent progress of such infants is excluded from the analysis of results. Trial failure infants and infants whose oral intake was <100 kcal/kg on day 14, on completion of the 2-week trial period, were offered parenteral nutrition supplements.

TPN group. A glucose amino-acid solution, based on Vamin N (Vitrum, Stockholm, Sweden) with added electrolytes, vitamins, and trace minerals was prepared by the pharmacy according to the programme shown in Table 1. TPN was prescribed on admission to the study beginning with formula 1A. The glucose infusion rate was increased from 8 to 18 g/kg per 24 hours in daily increments of 2 g/kg by upgrading from formula 1A to 3B if hyperglycaemia (blood glucose >11 mmol/l; >198 mg/100 ml) or glycosuria (Clinitest >0·5%) was not encountered. The programme allowed for an increase in the daily amount of amino-acid infused from 1 to 3 g/kg over 6 days. If there was glucose intolerance, the daily amount of glucose was adjusted, independent of the amino-acid intake. A soybean emulsion (Intralipid 20%, Vitrum, Stockholm, Sweden) was started at a level of 1 g/kg fat per 24 hours after recovery from neonatal jaundice (serum bilirubin <150 μmol/l (<8·8 mg/100 ml) and falling). This amount was increased, in the absence of visible lipaemia, to a maximum of 3 g/kg per 24 hours. If daily serum specimens showed more than a trace of lipaemia (equivalent to 2·8 mmol/l (250 mg/100 ml) triglyceride), lipid intake was reduced. The electrolyte content of the TPN solution was adjusted as shown by the biochemical status. As with infants in the Milk group, an intake of 150 ml/kg per 24 hours was generally provided, but this varied between 100 and 200 ml/kg depending on the clinical condition of the infant.

Infusion technique. TPN and supplemental glucose solutions (in the Milk group) were infused via the indwelling umbilical arterial catheter inserted in infants with respiratory distress or via peripheral veins when the former was not required. Catheter placement was in the descending aorta with the tip

Table 1 *Composition of TPN solution; amount infused (kg/24 hours)*

Component	*1*		*2*		*3*	
Standard components diluted in 24-hour fluid requirement (100–200 ml/kg)	*A*	*B*	*A*	*B*	*A*	*B*
Energy (kcal)	36	44	56	64	75	83
Glucose (g)	8	10	12	14	16	18
Amino-acids (g)	1	1	2	2	3	3
Na (mmol)			3·00–3·03			
K (mmol)			2·00–2·03			
Ca (mmol)			0·97–1·01			
Mg (mmol)			0·22–0·25			
P (mmol)			1·50–1·52			
Cl (mmol)			2·47–2·54			
Acetate (mmol)			0·35–0·75			
Bejectal + vitamin C (ml)			0·50			
Folic acid (mg)			0·38			
Phytomenadione (mg)			0·25			
Cu (μg)	—		+48·0		+ 95·0	
Zn (μg)	—		+94·0		+223·0	
Mn (μg)	—		+ 8·4		+ 16·6	
Cr (μg)	—		+ 3·9		+ 5·8	
Heparin (units)			125			

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*Similac has a composition close to that of human breast milk (protein 1·5 g/100 ml, fat 3·7 g/100 ml, carbohydrate 7·0 g/100 ml) prepared from nonfat cows' milk, vegetable oil, and added lactose.

at the level of the 3rd lumbar vertebra. An 0·22 μm Ivex 2 filter (Millipore, N.S.W., Australia) and an Ivac infusion pump (Watson-Victor, Victoria, Australia) were used for the glucose amino-acid infusion. Intralipid was infused continuously with a Harvard Syringe Pump (Stansen, Victoria, Australia) joining the glucose amino-acid mixture in a Y-connector distal to the filter and just proximal to the arterial catheter or intravenous needle. Infusates and administration sets were changed daily.

Monitoring. The infants were weighed daily to the nearest 10 g. Urine was analysed at least twice daily for osmolality and glucose. Serum osmolality, glucose, sodium, potassium, calcium, magnesium, chloride, phosphate, and bilirubin (total and direct); haemoglobin and haematocrit; and acid-base status were measured daily in the 1st week and on alternate days in the 2nd week of the study. The volume of blood required for these tests was 1·4 ml. The serum was also checked daily for visible lipaemia. Serum glutamic-oxalo-acetic transaminase, alkaline phosphatase, protein, urea, ammonia, lactate, transferrin, caeruloplasmin, and trace elements (Fe, Cu, Zn, Mn, Cr) were measured on days 7 and 14 of the study. The volume of blood required for these tests was 1·7 ml. Urine collection for 24 to 72 hours was done during the period of a nitrogen balance test.

Statistical evaluation. Significance of differences between fluid and nutrient intakes and body weight changes in infants on the two feeding regimens was determined using the Mann-Whitney U test.

Results

Clinical data and mortality. No significant difference in birthweights or gestational ages was noted between the 34 infants in the study and the 6 infants who died within 24 hours after birth (Table 2). Overall mortality for infants <1200 g was 32·5%. Seven of the 34 infants in the trial died (mortality rate 20·6%), 5 during the 2-week trial period and 2 in the 3rd week after birth.

The clinical data of the 17 infant pairs are summarised in Table 3. The groups were comparable in regard to birthweight and gestation. No infant had a birthweight under the 10th centile for gestational age. There were more boys, more infants with respiratory distress or apnoea, and more babies requiring oxygen or assisted ventilation in the TPN group compared with the Milk group. The differences were however, not significant. The mortality within the trial period in the TPN group (3 or 18%) was not statistically different from that in the Milk group (2 or 12%).

Four infants in the TPN group failed the trial. In one infant, the glucose amino-acid solution was not started within 3 days of birth because of severe metabolic acidosis from group B β-haemolytic streptococcal pneumonia. She subsequently recovered with treatment. The remaining 3 infants died during the course of the trial; 2 had intraventricular haemorrhages, one on day 3 and the other on day 5, and one baby had a pulmonary haemorrhage on day 14. A further infant in the TPN group died after the trial, on day 21, from an intraventricular haemorrhage.

Six infants in the Milk group failed the trial. One died on day 2 of an intraventricular haemorrhage and one died on day 14 as a result of necrotising enterocolitis. Three other infants developed necrotising enterocolitis on days 8, 10, and 12, all of whom recovered with treatment. One infant had aspiration pneumonia on day 14. A further infant in the Milk group died after the trial on day 19 of an intraventricular haemorrhage. Trial failures in the two groups are summarised in Table 4.

Intake. Data on volume and energy intake are shown in Table 5. The mean daily volume intake during the 1st week was 152 ml/kg per 24 hours in

Table 2 *Biographical data and survival rate of all infants <1200 g during study period*

Infants	*Birthweight (g)*	*Gestation (weeks)*	*Mortality*
	Mean±SEM (range)	*Mean±SEM (range)*	*No. (%)*
In study (n=34)	949±29 (570–1190)	26±0·4 (24–32)	7 (20·6)
Excluded from study (n=6) (deaths <24 hours)	973±73 (730–1195)	27±0·6 (25–29)	6
Total <1200 g (n=40)	953±26 (570–1195)	27±0·3 (24–32)	13 (32·5)

Table 3 *Comparison of clinical data and mortality for infants in the TPN and Milk groups*

	TPN (n=17)	*Milk (n=17)*
Birthweight (g)		
Mean ± SEM	922±39	976±42
Range	570–1180	660–1190
Gestation (weeks)		
Mean ± SEM	27±0·5	28±0·5
Range	24–32	24–32
Male to female ratio	11:6	7:10
Respiratory distress	13	11
Recurrent apnoea	4	3
Oxygen therapy	16	13
Assisted ventilation	16	11
Deaths during trial	3	2
Deaths after trial	1	1

Table 4 *Trial failures in the TPN and Milk groups*

Case	*Birth-weight (g)*	*Gestation (weeks)*	*Cause for trial failure*	*Day of trial failure*	*Outcome*
TPN					
1	730	24	Pneumonia and severe acidosis	3	Recovered
2	810	28	Intraventricular haemorrhage	4	Died on day 5
3	920	25	Intraventricular haemorrhage	3	Died on day 3
4	1040	29	Pulmonary haemorrhage	14	Died on day 14
Milk					
1	660	26	Intraventricular haemorrhage	2	Died on day 2
2	880	27	Aspiration pneumonia	14	Recovered
3	880	26	Necrotising enterocolitis	10	Recovered
4	1090	27	Necrotising enterocolitis	8	Recovered
5	1155	30	Necrotising enterocolitis	12	Recovered
6	1190	28	Necrotising enterocolitis	13	Died on day 14

Table 5 *Comparison of volume and energy intakes during the 1st and 2nd weeks in the TPN and Milk groups*

	TPN		*Milk*		*P*
	No.	*Mean± SEM*	*No.*	*Mean± SEM*	
Mean daily volume (ml/kg per 24 hours)					
1st week	17	152±4·4	17	152±3·5	NS
2nd week	14	149±5·9	16	167±3·5	<0·02
Mean daily energy intake (kcal/kg per 24 hours)					
1st week	17	55±3·8	17	63±3·8	NS
2nd week	14	104±3·3	16	88±6·4	NS
Age when desired energy intake attained (days)*	14	7±0·4	7	11±1·0	<0·05

TPN, 90 kcal/kg per 24 hours; Milk, 120 kcal/kg per 24 hours (Cashore *et al.*, 1975).
Conversion: traditional units to SI—1 kcal ≈4·185 kJ.

both groups. In the 2nd week, infants in the Milk group required significantly higher daily mean volume intakes compared with those in the TPN group in order to maintain normal hydration and serum osmolality. Milk provided an average of 62% of the volume intake on day 7 and 83% by day 14 (Fig. 1). With the exception of 3 infants who were fed exclusively on Similac and one infant who died before starting milk feeds, the remaining 13 infants in the Milk group were given fresh expressed breast milk, even though this was often complemented with Similac when the supply of breast milk was interrupted.

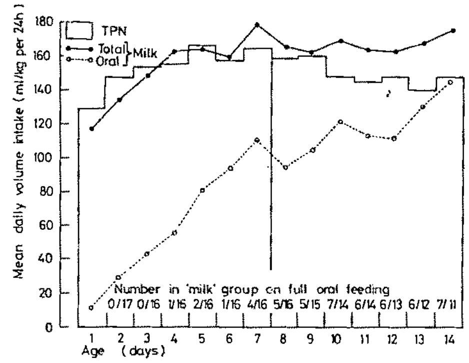

Fig. 1 *Comparison of volume intake in the TPN and Milk groups.*

The mean daily energy intake in the 1st and 2nd week was not significantly different in the two groups (Table 5). The number of infants and the ages at which they attained the desired energy intakes according to data of Cashore *et al.* (1975) were determined. 14 infants in the TPN group attained the parenteral desired energy of 90 kcal (380 kJ)/kg per 24 hours during the study period at an average age of 7 days compared with 7 infants in the Milk group who attained the oral desired energy intake of 120 kcal (500 kJ)/kg per 24 hours at an average age of 11 days. This difference was statistically significant. Milk provided an average of 78% of the energy intake on day 7 and 93% by day 14 (Fig. 2).

The mean daily carbohydrate, protein, and fat intakes in the two groups during the 1st and 2nd weeks are shown in Figs 3 and 4. There was a significantly higher intake of carbohydrates and protein in both weeks in the TPN group compared with the Milk group. 14 infants in the TPN group attained the desired protein intake of 2·6 g/kg per 24 hours during

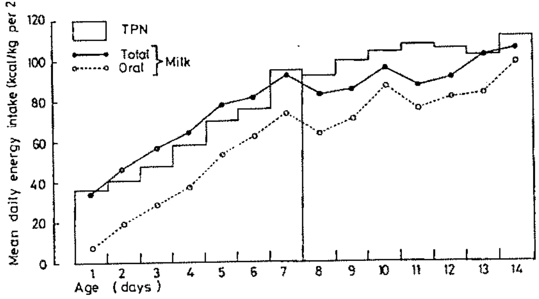

Fig. 2 *Comparison of energy intake in the TPN and Milk groups.*

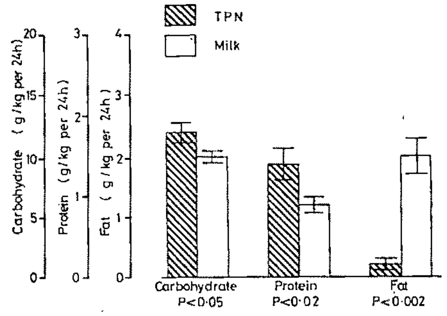

Fig. 3 *Comparison of carbohydrate, protein, and fat intakes during the 1st week in the TPN and Milk groups. Data expressed as mean ± SEM.*

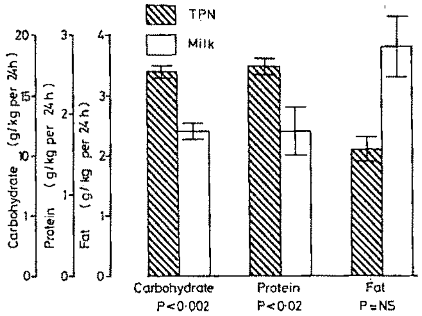

Fig. 4 *Comparison of carbohydrate, protein, and fat intakes during the 2nd week in the TPN and Milk groups. Data expressed as mean ± SEM.*

Table 6 *Comparison of postnatal weight changes of infants in the TPN and Milk groups*

	TPN		*Milk*		*P*
	No.	*Mean± SEM*	*No.*	*Mean± SEM*	
Mean daily weight loss in 1st week (g/day)	17	8±2·2	17	12±1·8	NS
Postnatal weight loss (% of birthweight)	17	11±1·4	17	12±1·7	NS
Age at lowest weight (days)	14	5±0·3	16	7±0·6	<0·02
Mean daily weight gain in 2nd week (g/day)	14	15±2·6	16	7±2·4	<0·02
Time to regain and maintain birthweight (days)	14	12±1·2	11	17±1·5	<0·05

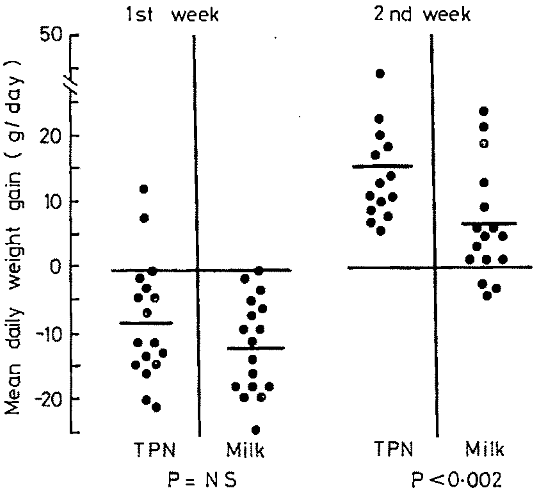

Fig. 5 *Comparison of postnatal weight changes for infants in the TPN and Milk groups. Horizontal bar shows mean values for each group.*

the study period compared with 9 infants in the Milk group. Mean daily fat intake during the 1st week was significantly lower in the TPN group compared with the Milk group. With infants in the TPN group, Intralipid was started only after recovery from neonatal jaundice at a mean of 7 days with a range of 5 to 11 days. No significant difference was observed in the mean daily fat intake in the 2nd week.

Weight changes. Table 6 and Fig. 5 show the weight changes for the two groups. There was no statistical difference in the mean daily weight loss in the 1st week and the maximum postnatal weight loss in the two groups. Infants in the TPN group began to gain weight sooner and faster compared with those in the Milk group, as shown by a significantly earlier age at lowest weight, a greater mean daily weight gain in the 2nd week, and a shorter mean time to regain and maintain birthweight. There was no statistical difference between the two groups in the age at which the infants attained 2000 g or the time of discharge from hospital. However, 3 of the 10 infants in the Milk group whose oral intake was still under 100 kcal/kg at the end of the 2-week trial were offered parenteral nutrition supplements, and 5 of the 27 survivors were transferred to the referring hospital for convalescent care before discharge. Such comparisons beyond the trial period are therefore difficult to interpret.

Complications. Metabolic disturbances are summarised in Table 7. Serum hyperosmolality was detected in 4 infants in the TPN group and in 2 in the Milk group. None of these infants developed intracranial haemorrhage. Hyperglycaemia was observed in both groups. All responded promptly to appropriate adjustments in the glucose infusion rate and insulin was not required. Electrolyte

Table 7 *Comparison of number of infants with metabolic disturbances during the study period in the TPN and Milk groups*

Serum values		*TPN*	*Milk*
Osmolality (mmol/kg)	>320	4	2
	<260	2	4
Glucose (mmol/l)	>11	9	6
	<1·5	0	1
Sodium (mmol/l)	>150	1	2
	<120	2	2
Potassium (mmol/l)	>8	1	1
	<3	2	2
Calcium (mmol/l)	>2·5	5	4
	<1·7	7	8
Magnesium (mmol/l)	>1·2	1	0
	<0·7	2	6
pH	<27·5	6	9
	>7·50	2	2
Base deficit (mmol/l)	>10	3	3
Lactate (mmol/l)	>2	2	0
Bilirubin (μmol/l)	>200	9	6
AST (μ/l)	>55	3	0
Alkaline phosphatase (μ/l)	>800	2	3
Proteins (g/l)	<40	3	5
Urea (mmol/l)	>8	1	0
Ammonia (μg/100 ml)	>150	0	1

Conversion: SI to traditional units—glucose: 1 mmol/l ≈ 18 mg/100 ml; calcium: 1 mmol/l ≈ 4 mg/100 ml; magnesium: 1 mmol/l ≈ 2·4 mg/100 ml; lactate: 1 mmol/l ≈ 9 mg/100 ml; bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml; urea: 1 mmol/l ≈ 6 mg/100 ml.

disturbances were comparable in both groups and were corrected as they appeared. TPN did not contribute significantly to the severity of metabolic acidosis compared with the conventional feeding method. Most infants in both groups developed hyperbilirubinaemia >150 mmol/l and required phototherapy. An increase in conjugated bilirubin was observed in 3 infants in the TPN group who also had raised AST levels at the end of TPN. One had cholestatic jaundice associated with postnatally acquired cytomegalovirus infection. There was a transient increase in the level of blood urea in one infant in the TPN group, and one infant in the milk group had one reading of a high blood ammonia level.

Bacterial or fungal septicaemia was not a complication in infants in either group during the study period. One infant in the TPN group who continued to require TPN for 10 weeks subsequently developed candida septicaemia but recovered on systemic amphotericin B.

Discussion

Results are given of a controlled study of 34 critically ill low birthweight infants, half of whom received intragastric milk feeding and, as necessary, IV glucose and electrolyte supplements. The other half received total parenteral nutrition. As the conventional practice is to establish an intra-arterial infusion on admission, infants in the Milk group all had IV glucose which supplemented the fluid and energy intakes during the period in which the volume of milk feeds was increased. It is therefore not possible to obtain a 'pure' milk feed group in infants under 1200 g. However it was considered that a true assessment of the advantages of parenteral nutrition for such infants could be gained only if the latter replaced milk feeding rather than supplemented it. Interpretation of previous reports of total parenteral nutrition is difficult in the absence of adequate controls fed conventionally under identical medical supervision. Studies have been biased by excluding infants with respiratory distress or those who required assisted ventilation (Driscoll *et al.*, 1972; Bryan *et al.*, 1973). Yet, these are the very infants who would particularly benefit from more calories and who are most difficult to feed orally. In the present study, infants were randomly assigned to a feeding method and none was excluded after starting the designated regimen.

Dweck and Cassady (1974) reported that hyperglycaemia was observed in 86% of very low birthweight infants receiving parenteral glucose. This was reported to be related to high glucose infusion rates exceeding 9·6 g/kg per 24 hours. Accordingly, the TPN regimen was designed to begin with a glucose load of 8 g/kg per 24 hours on day 1. It was possible, however, progressively to increase the mean glucose infusion rate within tolerance limits to 18 g/kg per 24 hours by 7 days after birth. The incidence of hyperglycaemia in the TPN group was similar to that in the Milk group. This complication was resolved by lowering the glucose infusion rate.

Formulated crystalline amino-acid mixtures are more effective than protein hydrolysates as the latter contain considerable amounts of small peptides that are not efficiently used. Of the crystalline amino-acid solutions, Vamin contains only L amino-acid isomers and is more efficiently used with respect to nitrogen metabolism than that containing both the D and L isomers, as in the case of Aminofusin (Pfimmer, Erlangen, West Germany), because of lower urinary amino-acid losses (Hendry *et al.*, 1978). Furthermore, Vamin maintains serum amino-acid concentrations that are close to normal in small premature infants (Shaw *et al.*, 1977), whereas Aminofusin seriously disrupts normal amino-acid concentrations (Kellerman *et al.*, 1976). The recommended dose of 3 g of amino-acids (equivalent approximately to 2·6 g protein)/kg per 24 hours given in this study, using Vamin as the nitrogen source, is based on work previously carried out here (Kellerman *et al.*, 1976; Shaw *et al.*, 1977; Hendry *et al.*, 1978). Heird *et al.* (1972a) suggested that the metabolism of excessive cationic amino-acids results in excess of hydrogen ion which leads to metabolic acidosis during parenteral nutrition. The incidence of this complication was low and similar in the TPN and Milk groups. It is possible that the acetate in the TPN solution acts as a bicarbonate precursor and is capable of buffering the excess hydrogen ion formed. Hyperammonaemia observed in infants given parenteral nutrition has been attributed to high ammonia content in protein hydrolysates or to inadequate arginine in the crystalline amino-acid solution (Heird *et al.*, 1972c; Johnson *et al.*, 1972). This complication was not observed in this study.

Less mature infants had a poorer Intralipid tolerance initially, as was observed by Shennan *et al.* (1977). However, most infants tolerated 3 g/kg fat per 24 hours by the 2nd week as had been shown previously (Cashore *et al.*, 1975; Gunn *et al.*, 1978). It has been noted, however, that some infants on Intralipid can develop high plasma levels of free fatty acids which can interfere with bilirubin-albumin binding and thus increase the risk of bilirubin encephalopathy (Andrew *et al.*, 1976). As we had no method for monitoring the effects of free fatty acids on bilirubin-albumin binding, it was decided that an increasing serum bilirubin level, or one >150 μmol/l, is a contraindication for Intralipid. This was found to occur in all the infants in this series within the first 5 days, thus contributing to the insufficient energy intake in the TPN group during this early period. Adequate monitoring of the Intralipid-bilirubin relationship by determining the reserve bilirubin-binding capacity or by calculating the free fatty acids to albumin molar ratio will provide a safety index for Intralipid use in the presence of neonatal jaundice.

The introduction of neonatal intensive care has led to a decrease in the mortality rate of very low birthweight infants (Stewart *et al.*, 1977). At the Queen Victoria Medical Centre, infants weighing <1000 g had over 80% mortality in the 3 years 1970 to 1972 (MacMahon *et al.*, 1975), whereas the mortality rates for those weighing 501 to 1000 g and 1001 to 1500 g were 52 and 20% respectively during 1977 (Yu and Wood, 1978). The reason for this improvement in outlook is obviously multifactorial, of which early adequate nutrition provided by safer methods is only one factor. An effect upon mortality can only be formally demonstrated by a carefully controlled study. However, it is impossible to isolate this one factor in the very low birthweight infant in whom the mortality will, in any case, be high. As in the one previous report of TPN versus a control group managed with the conventional feeding regimen (Gunn *et al.*, 1978), no statistically significant differences in mortality rate between the two groups could be shown. One factor which is not comparably matched in the two groups is the sex of the infants. The fact that there were 10 girls in the Milk group compared with 6 in the TPN group suggests that the Milk group was more favourably placed, allowing for the expected male preponderance in mortality.

Infants in the TPN group had earlier and greater weight gain than those in the Milk group, despite similar total caloric intake. Oral nutrients are poorly absorbed in preterm infants. The energy need in achieving weight gain observed in the present study is in agreement with that by Cashore *et al.* (1975) who reported that most infants gained weight at the expected rate of fetal growth *in utero* (20 g per day at 28 weeks and 30 g per day at 34 weeks) when the desired energy intake of 90 kcal(380 kJ)/kg per 24 hours of parenteral nutrition or 120 kcal(500 kJ)/kg per 24 hours of milk feeding was attained. Furthermore, the nitrogen intake of the Milk group was significantly lower than that of the TPN group for the duration of the study. In the 2nd week, the TPN group achieved the recommended parenteral nitrogen requirement of Vamin-fed preterm infants (Hendry *et al.*, 1978) of 30 mmol/kg nitrogen per 24 hours, equivalent to 3·1 g of amino-acids or 2·6 g/kg protein per 24 hours. The latter study also showed that only 80% of the oral nitrogen intake in these Similac-fed infants was absorbed, which put the infants in the Milk group at a further disadvantage. It has nevertheless been suggested that the faster weight gain observed in parenterally supplemented infants compared with their orally-fed controls might be attributable to water retention rather than to more rapid tissue accretion (Brans *et al.*, 1976); but in that study, there was no difference in daily protein intake between the two groups. Firm conclusions must await further studies, including concomitant estimates of total and extracellular body water.

Comparison of the morbidity in the two groups showed that no baby in the TPN group had necrotising enterocolitis whereas 4 infants in the Milk group developed this during the first 2 weeks, one of whom died despite surgical intervention for intestinal perforation. Enteric feeding, particularly for babies with mucosal ischaemia, was thought to be of aetiological significance in the development of necrotising enterocolitis (Yu and Tudehope, 1977). This has to be considered as a significant morbidity associated with milk feeding in very low birthweight infants in addition to the more commonly described aspiration pneumonia for which there was also one example in the Milk group in the present study. The incidence of intraventricular haemorrhage was similar in the two groups. None of the 5 infants with this complication had serum hyperosmolality but 4 of them, 2 in each group, had blood glucose levels >11 mmol/l. A further 11 infants were found to have transient hyperglycaemia but did not develop intraventricular haemorrhage. Though TPN in this study has not been shown to increase the incidence of hyperosmolality or hyperglycaemia compared with milk feeding, the clinical implication of hyperglycaemia in intraventricular haemorrhage (Dweck and Cassady, 1974) needs further study.

Metabolic complications were relatively common, but in no case were these persistent or considered to have resulted in serious consequences. The number of recorded disturbances could be attributed to the fact that the infants were closely monitored. Constant laboratory support, using microtechniques, was needed for early diagnosis so that rapid adjustments in the composition of the infusate could be made. However, it is reasonably certain that if monitoring had been less thorough or if a 'standard' mixture had been used, serious and perhaps fatal metabolic complications could have ensued.

This controlled study has shown a more adequate nitrogen intake and an improved weight gain, an avoidance of necrotising enterocolitis, but an unchanged mortality rate in very low birthweight infants managed with TPN compared with conventional milk feeding during the first 2 weeks after birth. Complications which could be specifically assigned to TPN were few. The possibility that TPN may be responsible for intrahepatic cholestasis in some very low birthweight infants is being investigated. Long-term studies of neurological, intellectual, and behavioural development are needed and are currently in progress.

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Numerical evaluation of facial pattern in children with isolated pulmonary stenosis

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SUMMARY A facial contouring technique, using light sectioning (Cobb, 1972), was modified (Ainsworth and Joseph, 1977) and used in a numerical study of children with isolated pulmonary stenosis (PS) to test the hypothesis that the facial pattern in this condition differs from the normal. Measurements were compared between a group of 20 normal children and a group of 20 children with PS between ages 6 and 10½ years. A distinctive facial pattern emerged. Many anteroposterior measurements were much greater in the PS group, indicating that the tissues were more prominent in the maxillary region. Altogether, 29 measurements showed significant differences ($P < 0 \cdot 05$) between the two groups. Discriminant analyses were carried out to discover which, if any, might be used to predict the group to which an individual should belong. Depending on the variables chosen, between 34 and 37 individuals from the total of 40 were assigned to the correct group—PS or control.

Detailed measurements of facial abnormalities in the child have not been made. A general subjective approach has usually been used which relies on the experience of the observer. The lack of suitable measuring techniques has been responsible for this approach.

Facial patterns are common in some congenital heart diseases, notably supravalvar aortic stenosis (Joseph *et al.*, 1966) and the cardiofacial syndrome (Cayler, 1969; Chantler and McEnery, 1971). It has been suggested that children with isolated pulmonary stenosis (PS) have moon faces (Wood, 1950), and Nadas (1963) referred to their round faces and broad cheeks. We too had a strong impression that patients with PS had a recognisable pattern and we wished to test this hypothesis by carrying out a detailed numerical analysis. An example of the facies in a child with PS is shown in Fig. 1.

The methods of moire fringe contouring (Takasaki, 1970) and stereophotogrammetry (Ainsworth and Joseph, 1976) were considered but finally a light-sectioning device (Cobb, 1972) which produced facial contour maps was chosen. It was used after modifications had been made.

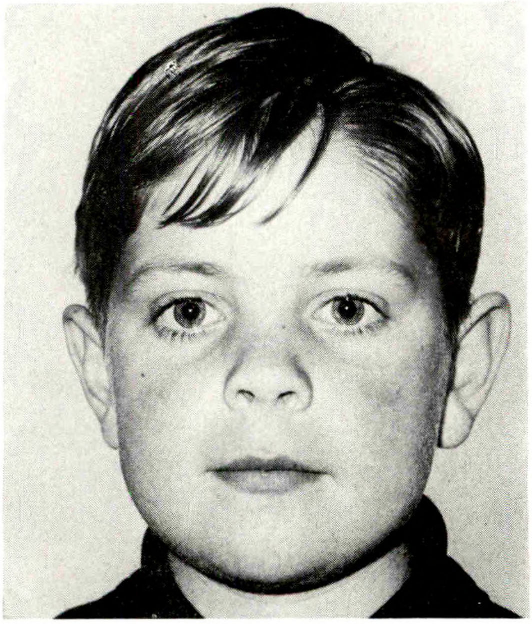

Fig. 1 *Facies in a child aged 8 years with isolated pulmonary stenosis.*

Subjects and methods

Contour maps were made of the faces of 20 children (boys and girls) with PS, confirmed by cardiac

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catheterisation or surgery. The patients came from Guy's and Brompton Hospitals. A control group of 20 normal children was obtained from Salomon's Centre, Guy's. Both groups of children were between ages 6 and 10½ years. The mean age of the PS group was 8 years (SD 1·66) and the mean age of the control group was 7·8 years (SD 1·42).

The contouring technique used has been described (Ainsworth and Joseph, 1977). Parallel slits of light were projected on to the subject's face, forming contours. They were photographed from a position perpendicular to their planes of projection. Plano-convex lenses, interposed in each optical path, prevented the light slits from diverging from their source and eliminated perspective distortion in the photograph. Full contour coverage of the face was achieved by rotating the head and taking multiple exposures. The exposures were orientated to a datum plane by an optical sighting system and linked by caliper measurements from life.

A life size contour map was drawn from each picture, producing a geometrically interrelated set of maps for each child. The sets of contour maps were processed by computer and sections of the face were drawn at the four levels, shown in Fig. 2, which also shows the landmarks used. The sections were confined to the maxillary region because we suspected that the most characteristic features of the pattern were in this area.

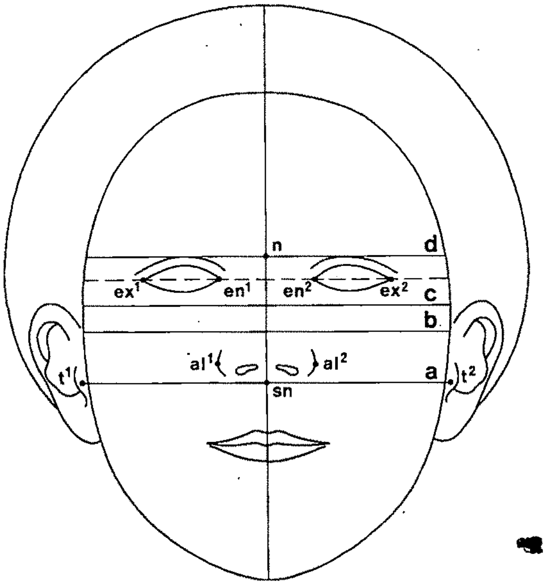


Fig. 2 *Landmarks and parallel planes of sections. Section (a) is defined by t^1, sn, and t^2. Section (b) is midway between section (a) and a horizontal line intersecting the canthi. Section (c) bisects the distance between section (b) and the canthi horizontal. Section (d) intersects (n).*

Table 1 *Measurements (A) of facial length, breadth, and height used for selecting the denominator of the facial index*

Measurements	*Fig.*	*No.*	*Control*		*Pulmonary stenosis*	
			Mean	*SD*	*Mean*	*SD*
Length	3	2	86·67	5·16	88·21	3·61
		63	74·50	3·85	76·25	4·02
Breadth	3	1	129·63	6·43	129·10	6·06
		41	124·90	6·73	124·30	6·03
Height	6	80	101·90	8·10	102·50	6·66

Facial proportion index. The variation caused by differences in facial size between individuals was eliminated by calculating ratios (R) rather than by giving actual measurements. By comparing real, or absolute measurements (A), a suitable dimension was selected, and in each face the remaining measurements were expressed as percentages of this dimension. This provided a proportion index which produced ratio (R) values and enabled a more precise comparison to be made.

Initial investigation was confined to measurements (A) of facial length, breadth, and height (Table 1). Length was expressed by two measurements at different heights in the midsaggital plane (2 and 63). Breadth was expressed by the intertragal dimension (1) and the bizygomatic diameter (41), and height by the distance between the nasion and gnathion (80). The most reliable measurement for use as the denominator of the facial proportion index was the intertragal dimension (1), since it was measured by calipers from life between distinct landmarks.

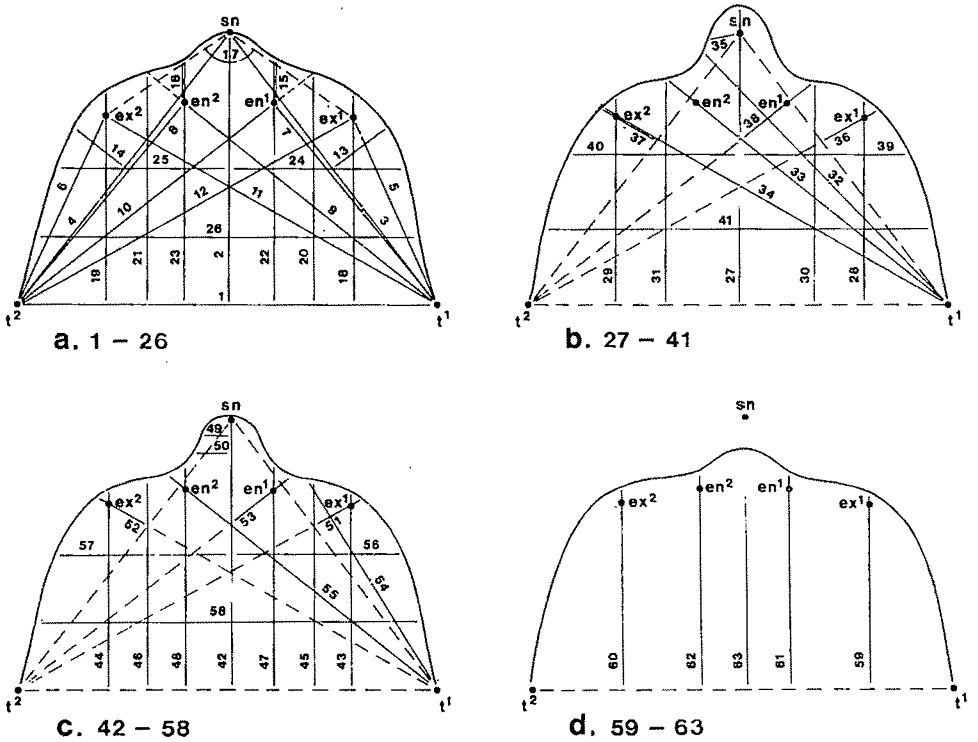
Thus the facial proportion index is:

$$\frac{\text{absolute measurements (A)} \times 100}{\text{intertragal measurement } t^1\text{—}t^2} = \text{ratio value (R)}$$

Results

Fig. 3 shows measurements 1–63 from which the mean values (R) for each group were used to construct composite sections at the levels (a), (b), (c), and (d). Broken lines represent the PS group, and continuous lines the control group (Fig. 4).

Sections (a). More measurements contributed to this pair of sections than to the other three pairs. Once the positions of the landmarks are established they remain common to all sections. It can be seen in Fig. 4 that the broken line is more prominent than the continuous one. In addition, in the PS group, the positions of both pairs of lateral and medial canthi



a. 1 – 26

b. 27 – 41

c. 42 – 58

d. 59 – 63

Fig. 3 *Measurements in sections (1–63). Continuous lines indicate the distances measured. Where a line is both continuous and broken, the continuous part represents the distance measured. Values for these measurements are shown in Tables 2, 3, 4,* and *5.*

and the subnasal landmark are also more prominent and consistently offset to the left. In Table 2 measurement 5 is significantly greater in the PS than in the control group ($P<0 \cdot 001$) and so are 3, 16, 18, and 20 ($P<0 \cdot 01$), as well as 7, 22, and 23 ($P<0 \cdot 05$). Measurement 17 is significantly less in the PS than in the control group ($P<0 \cdot 05$).

The offset positions of the landmarks affect diagonal measurements originating from the tragi. Measurements 3, 5, and 7 from t^1 are significantly different between the PS and control groups because the landmarks are offset in the direction of the measurements. The opposite measurements 4, 6, and 8 from t^2 are not significantly different because the landmarks are offset approximately at right-angles to the direction of the measurements. Consequently, in the remaining sections the measurements were chosen carefully to exploit fully the differences observed. Therefore, the majority of diagonal measurements originate from or are related to t^1.

Sections (b). The PS section is more prominent. In Table 3 measurement 28 is significantly greater in the PS than in the group ($P<0 \cdot 01$) as are measurements 27, 30, 32, 33, and 38 ($P<0 \cdot 05$).

Section (c). The PS section is more prominent. However, the actual shape of the section, irrespective of prominence, is distinctly different at the side of the nose. The curve is more gradual compared with the sharper and more angular shape of the control section. In Table 4 measurements 43 and 54 are significantly greater in the PS than in the control group ($P<0 \cdot 01$) and so are 42, 44, 45, 47, 48, and 53 ($P<0 \cdot 05$).

Sections (d). Five measurements are sufficient to identify the sections above the upper eyelids and through the nasion. A curve was drawn through the co-ordinates of each section. The PS section is more prominent. In Table 5 measurement 59 is significantly greater in the PS than in the control group ($P<0 \cdot 01$) and also 61 ($P<0 \cdot 05$).

Asymmetry. Of the 25 significant measurements between the PS and control groups in the sections,

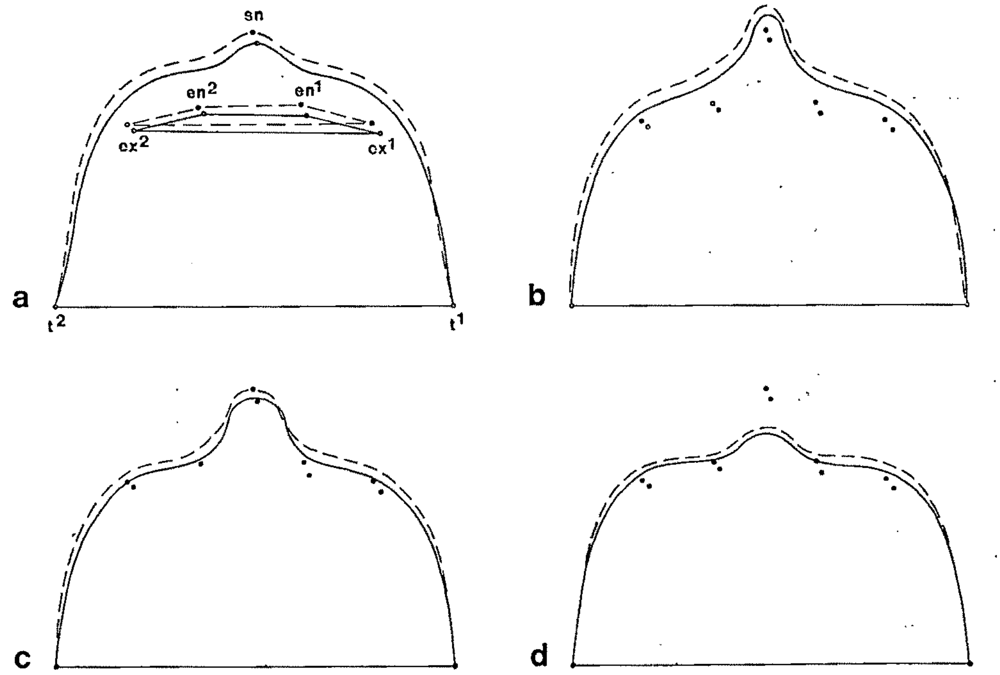


Fig. 4 *Composite sections, viewed from above, which were constructed from the mean (R) values in each group. Broken lines show the shape of the face in the PS group, and continuous lines show the shape of the face in the control group. In section (d), points representing the positions of the four canthi in each group have been joined. Broken lines indicate the PS group and continuous lines the control group.*

Table 2 *Ratio values of measurements in section (a) Fig. 3*

No.	*Control*		*Pulmonary stenosis*		*P*
	Mean	*SD*	*Mean*	*SD*	
1	100·00		100·00		
2	66·89	2·97	68·46	2·83	
3	82·98	2·13	85·35	3·01	0·007
4	83·61	2·39	84·99	3·07	
5	47·55	1·71	50·20	2·18	<0·001
6	48·66	2·40	49·22	2·01	
7	61·25	1·83	62·95	2·42	0·018
8	61·65	2·33	61·83	2·14	
9	79·86	3·23	80·90	2·63	
10	79·15	3·17	80·51	2·55	
11	92·49	2·60	92·82	2·82	
12	92·53	2·67	92·24	1·92	
13	17·39	1·66	18·28	1·85	
14	17·49	1·37	18·17	1·69	
15	10·71	1·48	11·38	2·03	
16	10·69	1·38	12·22	1·82	0·005
17	108·90	5·20	105·00	4·84	0·023
18	52·37	2·51	55·30	3·16	0·003
19	53·25	2·78	55·98	2·84	
20	56·83	2·36	59·23	2·87	0·007
21	57·20	2·84	58·89	3·63	
22	59·59	2·34	61·90	3·16	0·013
23	59·73	2·68	61·84	2·68	0·019
24	43·46	1·86	43·99	1·60	
25	43·34	1·50	43·45	1·41	
26	93·14	1·72	93·11	1·70	

Table 3 *Ratio values of measurements in section (b) Fig. 3*

No.	*Control*		*Pulmonary stenosis*		*P*
	Mean	*SD*	*Mean*	*SD*	
27	72·55	2·44	74·79	3·31	0·020
28	48·57	1·61	51·43	3·46	0·004
29	49·23	2·61	51·05	3·10	
30	53·65	2·77	56·36	3·73	0·014
31	53·68	2·88	55·45	3·20	
32	84·48	1·93	86·53	2·78	0·011
33	86·89	2·23	89·05	3·23	0·020
34	96·29	2·53	98·15	3·28	
35	7·42	1·22	7·87	0·90	
36	15·63	1·37	16·54	1·80	
37	16·07	1·99	16·72	2·12	
38	23·10	2·59	25·34	2·67	0·014
39	43·28	1·69	43·92	1·85	
40	43·78	1·70	43·29	2·20	
41	96·36	2·68	96·31	1·96	

there are 17 which have opposite measurements (not necessarily correspondingly significant) in the same relative positions on the other side of the face. Four of these are on the left side of the face (16, 23, 44, and 48), and 13 are on the right (3, 5, 7, 18, 20, 22, 28, 30, 43, 45, 47, 59, and 61). There are more significant

Table 4 *Ratio values of measurements in section (c) Fig. 3*

No.	*Control*		*Pulmonary stenosis*		*P*
	Mean	*SD*	*Mean*	*SD*	
42	66·68	2·82	66·88	2·69	0·017
43	45·38	2·48	48·53	3·06	0·001
44	46·11	2·63	47·99	2·84	0·039
45	48·71	4·03	51·65	2·81	0·012
46	50·06	2·68	51·11	2·78	
47	52·46	2·97	54·64	3·27	0·036
48	52·23	2·62	54·29	2·64	0·026
49	6·69	1·90	5·95	0·92	
50	8·87	1·36	9·09	0·91	
51	13·09	1·54	13·90	1·68	
52	13·01	2·56	13·60	1·92	
53	19·30	2·32	21·07	2·19	0·019
54	57·25	1·96	59·56	2·88	0·006
55	82·96	2·08	84·34	3·08	
56	43·11	1·13	43·79	2·66	
57	42·81	1·70	42·65	2·26	
58	96·54	2·96	96·39	2·34	

Table 5 *Ratio values of measurements in section (d) and other regions*

Region	*Fig.*	*No.*	*Control*		*Pulmonary stenosis*		*P*
			Mean	*SD*	*Mean*	*SD*	
Section (d)	3	59	47·53	2·39	50·27	2·60	0·002
		60	48·15	2·89	48·96	2·55	
		61	50·43	2·82	52·35	2·58	0·033
		62	51·74	3·42	52·77	3·25	
		63	57·55	3·07	59·13	3·38	
Eyes	5	64	18·93	1·00	18·61	1·06	
		65	18·76	1·10	18·73	1·08	
		66	25·29	1·88	24·91	1·74	
		67	61·71	2·86	61·33	3·06	
		68	6·08	1·24	7·06	1·27	0·018
		69	6·23	1·25	6·79	1·28	
		70	2·82	0·91	2·60	0·76	
		71	2·91	1·00	2·83	0·68	
Nose	5	72	23·17	1·78	24·44	1·61	0·023
		73	31·91	2·12	32·87	2·36	
		74	32·96	2·09	34·16	2·02	
		75	32·73	1·83	34·08	2·69	
Nose	6	76	14·99	2·20	16·02	2·16	
		77	13·74	2·08	13·05	3·26	
Lateral	6	78	194·90	5·01	195·50	3·70	
		79	86·99	2·83	85·84	1·88	
		80	78·52	3·74	79·74	4·72	
		81	53·38	1·60	56·10	1·97	<0·001
		82	66·10	1·63	67·72	2·28	0·017

measurements on the right; this suggests that an asymmetrical pattern is present.

In each group asymmetry was measured by the differences between corresponding measurements on opposite sides of the face. The two most interesting pairs are 5 and 6, and 59 and 60, which both show differences at the 1 % level between the two groups.

The opposite asymmetrical tendencies of both groups explain why, when coupled with greater anteroposterior measurements in the PS group, the majority of differences in the sections are on the right.

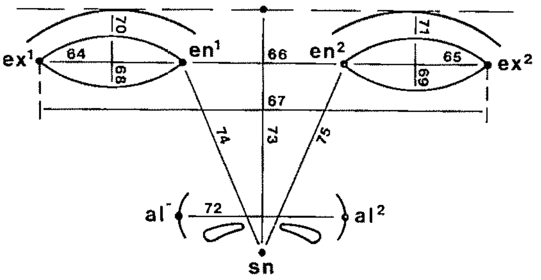


Fig. 5 *Measurements relating to the eyes and nose (64–75). Values for these measurements are shown in Table 5.*

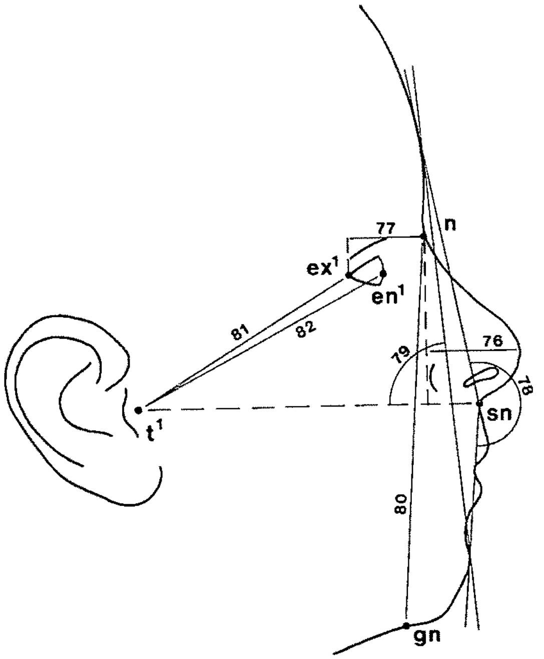


Fig. 6 *Lateral measurements in the midsaggital plane (76–80) and in 3 dimensions (81 and 82). Values for these measurements are shown in Table 5.*

Eyes, nose, and side of the face. The values for measurements associated with these components are shown in Table 5. Fig. 5 identifies measurements 64–75, and Fig. 6 identifies measurements 76–82. The height of the right palpebral fissue (68) is greater in the PS group (P<0·05).

The maximum width of the lower portion of the nose between the alae (72) is greater in the PS than in the control group (P<0·05). There is little difference in the length of the nose (73), although in the PS group it is slightly longer as are the other measurements of nasal length (74 and 75). Prominence of the tip of the nose (76) is marginally greater in the PS group. The bridge of the nose at the nasion (77) is similar in both groups.

The maxillary angle (78) is similar in both groups. The facial angle (79) is particularly so. There is no difference in the measurement of facial height (80). The 3-dimensional distance between t^1 and ex^1 (81) is significantly greater in the PS than in the control group ($P<0·001$). The 3-dimensional distance between t^1 and en^1 (82) is also significantly greater in the PS than in the control group ($P<0·05$).

Statistical analysis. Of the 83 variables, 29 showed significant differences at the 5% level. This suggests that, for a particular individual, it may be possible to predict to which group, control or PS, he is likely to belong. The theory of discriminant analysis (Fisher, 1938; Rao, 1952; Hills, 1966; Armitage, 1971) gives rules for constructing a function of a set of variables, such that the sign (positive or negative) of the value of the function predicts the group (control or PS).

The best set of two variables consisted of 5 and 16. Their values are represented by points on a scatter diagram (Fig. 7). Points above the line correspond to positive values of the discriminant function—that is, individuals classified into the PS group. Four children with PS were misclassified as belonging to the control group, and one child was misclassified as belonging to the PS group.

The classification can be improved by using more variables. In Fig. 8 histograms for each group are shown for six variables.

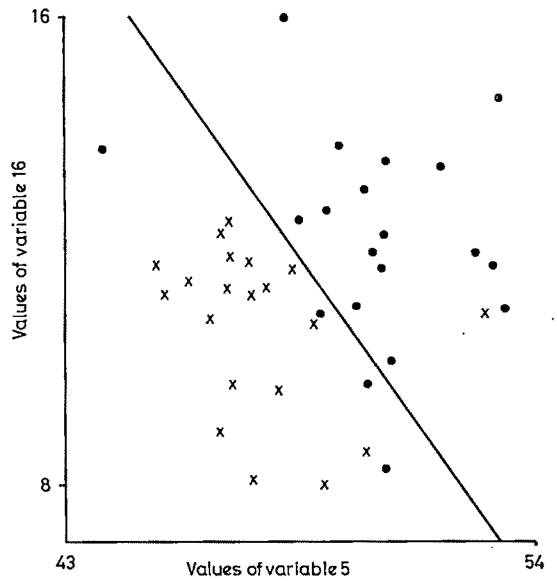


Fig. 7 *Discrimination from two measurements between the group of control children (X) and group with PS (●).*

The error rate of a discriminant function—that is the proportion of individuals it will misclassify—may be estimated by applying it to both groups of children. This will underestimate the error rate to be expected when used on other individuals, as the discriminant function has been chosen as the best for the sample groups. The estimate of Lachenbruch (1965) avoids this bias and gives a more accurate estimation. This is shown in Table 6 for several sets of variables. The error rate for six variables is now estimated as 4, as opposed to 2 in Fig. 8, where Lachenbruch's estimate was not applied.

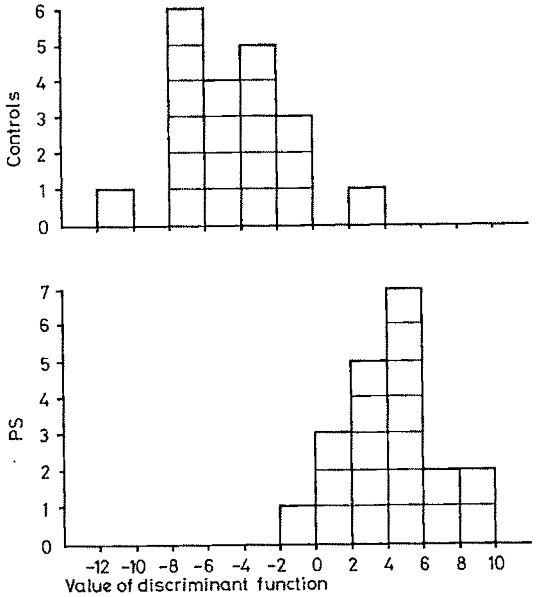


Fig. 8 *Histogram of discriminant function of variables 5, 16, 33, 44, 47, and 59.*

Table 6 *Error rates of the discriminant function*

No. of variables	*Delta Δ*	*Lachenbruch's estimate*		*Variables*
		Proportion	*Expected number of mis-classifications*	
2	1·91	0·125	5	5, 16
5	2·68	0·15	6	5, 16, 33, 44, 47
5	2·65	0·15	6	7. 16, 68, 81, 82
6	2·93	0·1	4	5, 16, 33, 44, 47, 59
8	3·20	0·075	3	7. 16, 17, 30, 45 53, 81, 82
10	3·65	0·075	3	5, 16, 17, 23, 28 30, 33, 44, 47, 59

Discussion

Statistical analysis proves that children with PS have a distinctive facial pattern. Measurements can discriminate between both sample groups, classifying between 34 and 37 of the total of 40 children as either PS or control, according to the number of variables used.

All anteroposterior measurements in the sections, whether significant or not, are greater in the PS than in the control group. The majority emerge from a common source, a vertical plane coincident with the intertragal dimension t^1–t^2 (intertragal base plane).

In the PS group the face is longer from the intertragal base plane. A notable feature is the prominence of the subnasal and canthi landmarks, with correspondingly more prominent sections. However, the relationship between the forward landmarks in both groups, and the maxillary region considered in isolation without reference to the intertragal base plane, is much more subtle. For example, the positions of the four canthi, relative to each other in each group, are almost identical. Consequently, it is appropriate to consider the differences in two ways. Firstly, to devote special attention to the maxillary region, ignoring its relationship with the intertragal base plane, and secondly, to consider overall differences relative to the intertragal base plane which are responsible for the increase in facial length of the PS group.

Maxillary region. Comparisons can be made using the composite sections as a visual guide, but superimposing the canthi. The sections (a) for each group are different in shape. The PS section shows that the cheeks are slightly wider and more rounded. Measurement 16, which is highly significant, supports this and shows that there is a more prominent distribution of soft tissue in the cheeks continuing round to the sides of the nose adjacent to the alae. The position of the PS subnasal landmark (sn) is more prominent, and the angle ex^1 sn ex^2 (17) is less in the PS than in the control group, indicating more tissue at this point in front of the maxilla. This general 'bulge' becomes less pronounced in the other sections, but nevertheless is supported by two significant measurements, 38 in section (b) and 53 in section (c). The tissue covering the zygomatic bone resumes the same form as the control group.

In the region of the nose, the curve of the PS section (c) is more gradual than the steeper and more angular curve of the control section. Measurement 53 supports this. The sides of the nose near the bridge seem to be filled with excess soft tissue. This trend continues down the sides of the nose becoming less and finally ending in a significant increase in the width of the nose between the wings (72). There is probably more cartilage at the sides of the nose and the tissue of the alae is more developed laterally.

Although the palpebral fissures are the same length and distance apart in both groups, the height of the right palpebral fissure (68), being significantly greater in the PS than in the control group, gives the eye a more rounded appearance with a slight decrease in height of the right upper lid. It is possible that a similar impression is produced in the left eye, but the actual measurements are not very different.

It can thus be seen that the differences in the maxillary region indicate different distributions of tissue in the PS group.

Anteroposterior differences. The much greater anteroposterior dimensions in the PS group could be caused by the maxillary region advancing anteriorly as a result of (1) excess tissue in that region only, or (2) excess tissue in the maxillary region, combined with a longer skull. Alternatively, the tragi may be situated more posteriorly as a result of (3) excessive posterior growth of the tragi, or (4) the complete ear is set back by a longer skull displacing the external auditory meatus. There could be a combination of these factors. However, it is clear that the differences are due either to soft or hard tissue, or to a combination of both. A definite conclusion, even with a detailed analysis of the skull, would be difficult to reach because different combinations of abnormal components can produce the same effect. Nevertheless, several points are worth noting.

If (1) is wholly or largely responsible, and the eyeballs remained in the same relative position to the intertragal base plane in both groups, the length of the palpebral fissures in the PS group would be very much less. The measurements confirm they are not. Therefore the eyeballs would have to be more forward in the orbits to bring their perimeters out to the more prominent positions of the PS canthi, which would be displaced anteriorly from the lacrimal and zygomatic bones due to a substantial increase in tissue around the eyes. This would mean that the eyeballs are being forced forwards in their orbits.

If (2) is responsible, the eyeballs would remain in the same relative positions to their orbits, and the canthi would be much the same distance from the bone in both groups.

It seems unlikely that (3) is involved to a large extent, as the ear would assume a very odd appearance which we did not observe.

It has been shown that a more prominent distribution of tissue in the maxillary region accounts for a portion of the increase in facial length in the PS group. We think it is probable that, quite apart from altering the appearance and shape of the face in this region, an excess of tissue distributed throughout this area is wholly responsible for the greater anteroposterior measurements in the PS group.

Relationship to other organs. Since the face is repeatedly being looked at, the observer becomes skilled in discriminating between differing facial patterns. It is the subtle blending, structural form, relative sizes and shapes of the parts of the face which are responsible for differing facial patterns. In diseases not apparently affecting the form of the face, knowledge of its morphology may still be relevant. Thus it is conceivable that more subtle variations in the anatomy of the face are present which can be identified only by precise measurements. The face could be affected by some of the disturbances which have occurred in other organs during development.

In the normal developing fetus we do not know whether the embryological parts progress independently in an unrelated order, or fit into a precise system in an accurately timed sequence. If our tissues and organs do depend on one another for their origin and form, then we must base our observations on analysis of the embryo as a whole rather than restriction to individual organs. Any marked departure from normality in one organ might therefore be accompanied by maldevelopment in many other organs. Thus the facial pattern in children with PS may be an example of this interdependence of the form of various organs.

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Vertical transmission of hepatitis B surface antigen in carrier mothers in two west London hospitals

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SUMMARY 126 children of 102 hepatitis B surface antigen (HBsAg) carrier mothers were delivered at Hammersmith Hospital and Queen Charlotte's Maternity Hospital, between 1971 and mid-1978. Blood tests on 110 of these children showed that 8 out of the 18 with Chinese mothers, but only 6 out of the 92 other children, have become HBsAg positive. The presence of maternal hepatitis B e antigen (HBeAg) is also significantly correlated with transmission of HBsAg to the children. The management of children whose mothers are carriers is discussed.

Since the discovery of hepatitis B antigen (Australia antigen) in 1965 leading to the identification of the causative agent of hepatitis B (Blumberg *et al.*, 1965; Prince, 1968; Krugman and Giles, 1970), awareness of its position as a major source of both acute and chronic disease has been growing (Ohbayashi *et al.*, 1972; Kattamis *et al.*, 1974; Dupuy *et al.*, 1975; Welsh *et al.*, 1976). Sensitive and rapid tests for the detection of the whole virus (HBV) and its components, the surface antigen (HBsAg) and core antigen (HBcAg) are now available, and these have contributed to our knowledge about the prevalence and modes of transmission of HBV. Besides these antigenic particles and their corresponding antibodies (anti-HBs and anti-HBc), other markers have been found in association with HBV, notably hepatitis B 'e' antigen (HBeAg) and anti-HBe (Magnius *et al.*, 1975).

It is known that the prevalence of HBV varies geographically, and is estimated to be 0·1% in northern Europe and North America, but up to 20% in Taiwan (Shih *et al.*, 1971; Gerety *et al.*, 1974; Helske, 1976; Chen and Sung, 1977). Modes of spread of the virus include direct or accidental inoculation of infected blood or blood products through transfusion, intravenous drug abuse, tattooing, acupuncture, dental work, shared razors, laboratory accidents, and perhaps insect vectors (Metselaar *et al.*, 1973; Patterson *et al.*, 1974), sexual contact (Heathcote *et al.*, 1974b), and 'vertical' transmission from mother to baby (Turner *et al.*, 1971; Merrill *et al.*, 1972; Papaevangelou *et al.*, 1974; Anderson *et al.*, 1975; Stevens *et al.*, 1975), probably through ingestion or passage of blood through broken skin or mucous membranes during delivery. Most body fluids, including saliva (Bancroft *et al.*, 1977), sweat (Telatar *et al.*, 1974), semen (Heathcote *et al.*, 1974a), pleural fluid (DeFlora and Forci, 1977), breast milk (Krugman, 1975), and blood may contain the virus. Horizontal spread in ways other than through blood seems likely but has not been well defined (Szmuness *et al.*, 1975).

As the virus is able to persist in man for long periods (after acute hepatitis or without detectable illness), producing so-called 'carriers', defined as those in whom HBsAg is present for more than 6 months (World Health Organisation, 1977), it would appear that a large reservoir may preclude its eventual eradication.

Through screening and the gradual elimination of HBsAg-positive carriers from panels of blood donors, once an important source of hepatitis, vertical transmission may rapidly become the principal means of viral spread, especially in countries with a large number of carriers. One report (Derso *et al.*,

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1978) indicated that certain ethnic groups, particularly the Chinese, may be genetically prone to such transmission, and the increased risk does not appear to be related to the birthplace of the mother but to her ethnic origin. We report here a study based on all the infants delivered of HBsAg-positive carrier mothers at two hospitals in west London, the Hammersmith Hospital and Queen Charlotte's Maternity Hospital. This study appears to confirm earlier work. Some of the mothers from the Hammersmith Hospital were the subject of a previous report (Waterson *et al.*, 1977).

Methods and subjects

Since July 1971 at Hammersmith Hospital, and since January 1972 at Queen Charlotte's Maternity Hospital, all antenatal patients have been screened for the presence of HBsAg. From those dates up to August 1978, a total of 102 HBsAg-positive carriers have been detected who subsequently delivered 126 live infants. There were no stillbirths. The total number of deliveries during those periods in the two hospitals was 33 467, giving a prevalence of 0·4 per 1000 deliveries. Ten abortions, 6 acute cases of hepatitis, and 6 cancelled bookings of carrier mothers have been excluded, as we were only interested in liveborn infants of carriers.

Cord blood samples were sent in the early years of the study for HBsAg screening by gel diffusion or immunoelectrophoresis, and after 1974, by direct passive agglutination (Hepatest, Wellcome). In a few cases that were positive, a sample of the baby's blood was also tested. 60 cases in which the cord blood was negative were also sent for radioimmunoassay (RIA) testing (at the Public Health Laboratory Services, Colindale, London).

Between February 1972 and May 1974, 8 randomly selected infants whose cord bloods were negative were given 1 ml (100 mg) of hepatitis B immune globulin (HBIG) at birth, and one was given 2·5 ml at birth. A further 10 infants were given 1 ml of HBIG at birth with a single repeat of this dose between 2 and 8 months, if blood was still negative for HBsAg. This trial was stopped in 1974.

Breast feeding was allowed freely, as we agree with other workers (Beasley *et al.*, 1975) that transmission of virus through breast milk and/or ingestion of blood from excoriated nipples is negligible compared with the infant's exposure to contaminated maternal blood at delivery and subsequent close contact at home.

Mothers were asked to bring their children to the clinic at intervals up to age 2 years for testing of HBsAg, both of their infants and themselves. The infant's liver function tests were also requested if sufficient blood had been obtained.

In August 1977, an effort was made to recall all the children for physical and developmental examinations and repeat blood specimens. Liver function tests were obtained if possible, and in about half of the cases, if blood was negative for HBsAg by Hepatest, a sample was sent for further RIA testing (PHLS, Colindale).

93 of the 102 mothers were also tested for the presence of HBeAg and anti-HBe by agar gel diffusion (by M. Supran, PHLS).

Results

Mothers. The birthplaces and ethnic origins of the 102 carrier mothers and the numbers of children are given in Table 1. No mother had clinical signs of hepatitis at any time during pregnancy or follow-up. Of 58 mothers who had liver function studies done, 5 had abnormal results at least once, and of these, one was positive for HBeAg, one positive for anti-HBe, and 3 were not tested for either.

It is of interest to note that 21 of the 102 mothers had worked in hospitals before the discovery of their HBsAg carrier state. Several were nurses who had had contact with jaundiced patients or those undergoing haemodialysis.

Table 1 *HBsAg-positive carrier mothers*

No. of mothers (n = 102)	*Ethnic origin*	*Places of birth*	*No. of children delivered (n=126)*	*No. followed up (n = 110)*	*No. HBsAg+ after 1st week (n = 14)*
15	N. European	France, Poland, Uganda, UK	17	14	2
13	S. European	Cyprus, Greece, Italy, Yugoslavia	17	14	0
3	N. African	Egypt, Morocco	4	4	0
41	W. African	Aruba, Gambia, Ghana, Grenada, Guyana, Jamaica, Nevis, Nigeria, St Kitts, Sierra Leone, Trinidad, UK, USA	51	44	3
1	E. African	Uganda	1	1	0
19	E. and S.E. Asian	Brunei, Hong Kong, Japan, Malaysia, Mauritius, Philippines, Singapore	23	20*	8†
5	S. Asian	Bangladesh, Guyana, India, Pakistan, Trinidad	6	6	1
5	S.W. Asian	Iran, Iraq	7	7	0

*18 had Chinese mothers, †all had Chinese mothers.

Table 2 *HBeAg status of 93 mothers and HBsAg status of their children*

Mother's status (n=93)		*Children*		
		HBsAg+	*HBsAg−*	*Unknown*
HBeAg+	10 (7 Chinese)	9	3	2
Anti-HBe+	38 (2 Chinese)	3	42	2
Neither found	45 (5 Chinese)	2	45	9

The HBeAg status of the 93 mothers tested for this is given in Table 2. Chinese mothers are much more likely than nonChinese mothers to be HBeAg positive ($P<0{\cdot}001$). Eight of the 10 HBeAg-positive mothers produced 9 of the 14 HBsAg-positive children. Of the remaining 2 HBeAg-positive mothers, one was Japanese and had 3 children, all HBsAg negative. We were unable to follow up the child of the other mother.

Children. Of the 126 children 53 (43%) were girls. We were able to see 110 after the first week of life. The mean age of follow-up was 24·8 months (range 2 months to 5 years 9 months). Three of the remaining 16 had died (one due to congenital heart disease at age one week, and 2 due to cot deaths at ages 3 and 16 months), and 12 could not be located or had parents who refused to allow blood to be taken. From one child, in Malaysia, a blood sample could not be obtained in spite of several attempts.

The results of cord blood testing are given in Table 3.

14 (13%) of the 110 children were later HBsAg-positive, 4 by RIA testing only. Details are given in Table 4. Five of the 14 were girls. All the children were growing and developing normally, and no hepatomegaly was found. Alanine transaminase (ALT) results were normal in the 9 positive children who were tested. Two of the 14 positive children had received 1 ml of HBIG at birth only; the rest received none. Table 4 shows that 8 of the 13 mothers were positive for HBeAg, and in fact 7 of these 8 were Chinese. In 2 of these Chinese families, both with HBeAg-positive mothers, we were able to test siblings; in one, the sibling was found to be positive, while in the other, she was negative. Six of the 13 fathers were tested and all were HBsAg negative.

Table 3 *Positive cord bloods*

Cord blood		*Children*		
Positive on initial screen	*Positive by RIA only*	*Later HBsAg+*	*Later HBsAg−*	*Lost to follow-up*
9		1	6	2
	10*	3	7	0

*One child positive by RIA only at birth was positive by Hepatest at 2 months, but negative by both RIA and Hepatest at 6 months.

Table 4 *HBsAg-positive children*

Case	*Mother's birthplace*	*Mother's ethnic origin*	*Age first+ (months)*	*Cord+?*	*Mother's HBe status*
1*	UK	N. European	15†	No	anti-HBe
2*	UK	N. European	2	No	Neither
3	Nigeria	W. African	6	No	anti-HBe
4§	St Kitts	W. African	36‡	No	HBeAg
5§	St Kitts	W. African	30‡	No	HBeAg
6*	Bangladesh	S. Asian	30‡	Yes	Neither
7*	Malaysia	Chinese	1½	No	anti-HBe
8	Hong Kong	Chinese	16‡	No	HBeAg
9	Mauritius	Chinese	1½	Yes	HBeAg
10	Hong Kong	Chinese	3	No	HBeAg
11	Hong Kong	Chinese	7	No	HBeAg
12	Malaysia	Chinese	5	No	HBeAg
13	Malaysia	Chinese	3	Yes	HBeAg
14	Singapore	Chinese	5	Yes	HBeAg

*Positive by RIA testing only; †negative at 3, 6, and 12 months by RIA, but positive at 15 and 24 months by RIA; ‡these children were not tested before these ages; §siblings.

As noted in Table 4, one of the children (Case 1) was negative when tested at ages 3, 6, and 12 months, but at ages 15 and 24 months she was RIA positive. This may indicate some form of horizontal transmission. Her father was negative for HBsAg.

There was no significant difference in the incidence of breast feeding between the groups of positive and negative children.

Discussion

Our results reflect the mixed ethnic origins of the population in London and seem to confirm the findings of others regarding a racial tendency to vertical transmission of the HBV, as detected by the presence of HBsAg. There have been interesting theories regarding the genetics of such transmission (Hug, 1976; Blumberg, 1977).

Some recent work has dealt with the sex distribution of carriers, as more men than women are carriers (Goodman *et al.*, 1971; Curtis *et al.*, 1973), and it also seems that where one parent is a positive HBsAg carrier, there is an increased secondary sex ratio (number of males per 100 females) (Drew *et al.*, 1978). Our 102 mothers have produced, to our knowledge, a total of 223 children, 125 (56%) boys and 98 (44%) girls. The numbers are too small for valid analysis, however, and complete data are not available.

Our cord blood results, as those of others (Aziz *et al.*, 1973), would appear to show the unreliability of such specimens in predicting the future HBsAg status of the child. Contamination with maternal blood may account for most if not all positive cord bloods; in several cases in which cord blood was positive, a blood sample from the infant was checked and found to be negative. In fact, at Hammersmith Hospital cord blood testing is no longer done;

instead a specimen is taken from the child some time during its first week of life. *In utero* transmission has been reported but is thought to be rare (Schweitzer and Spears, 1970), and usually comes not from carrier mothers but from overt cases of hepatitis during the last trimester of pregnancy or early in the postpartum period (Schweitzer *et al.*, 1972, 1973).

The HBeAg positive state of the mother increased the transmission of HBV to the child, as has been shown by others (Beasley *et al.*, 1977; Chaudhuri *et al.*, 1977; Gerety and Schweitzer, 1977; Murata *et al.*, 1977). Anti-HBe was not necessarily protective, as can be seen from Table 2, although this has been suggested (Okada *et al.*, 1976). There are those who now say that HBeAg may not be a marker of HBV but an indication of liver damage (Fay *et al.*, 1977; Tiku *et al.*, 1977; Vyas *et al.*, 1977); we did not have adequate maternal liver function studies to be able to corroborate this.

The infants, therefore, who were at greatest risk from vertical transmission of HBV in our study were those whose mothers were Chinese and/or HBeAg positive. This raises the question of passive protection such as that recommended by the World Health Organisation (1977) for a single acute exposure—one might argue that during parturition this is the type the child receives. The two positive children who received only a single dose of HBIG at birth might have benefited from larger, repeated doses (Dosik and Jhaveri, 1978; Iwarson and Norkrans, 1978). It is concluded that an adequate trial of HBIG prophylaxis is not feasible in London or elsewhere in the UK, where there are so few carrier mothers.

Concerning the continued surveillance of the children with HBsAg-positive mothers, we would agree with those (Melnick *et al.*, 1976; Woolf and Williams, 1976; Barker *et al.*, 1978) who feel blood should be tested at birth, 6 months, and 12 months, and if the child remains negative, he could be discharged (although we did have one conversion after this age). In the case of children found to be positive, yearly examinations and liver function tests for life ought to be considered. This would not necessarily be adequate in diagnosing chronic active hepatitis or hepatocellular carcinoma, but at least one's index of suspicion would be high. It would seem that very long-term follow-up studies will be needed before questions such as the necessity for frequent liver biopsies can be answered adequately. Management of the carrier has been discussed at length (Cossart, 1977).

Mothers, too, ought to be referred for follow-up in medical clinics once their obstetric need has ended (Babb, 1976). We found that few of the women were seen regularly except for antenatal care. We tended to be reassuring about good future health, despite the mounting evidence of possible liver disease later, as almost all our mothers were very upset at the idea of being 'infectious' and a few felt constrained in handling their new babies.

Mothers were warned about the need for care in handling their own blood from any source, as well as the need to inform their dentists and anyone who might later seek blood samples (general practitioners were officially informed). When a child was found to be positive we gave similar advice, but have found that perhaps the child's positive status should not be mentioned at school, as he may then be regarded with suspicion. One 6-month-old child in our study was rejected by a nursery as a result of this information, probably due to fear and ignorance by the nursery staff. There have been studies in schools indicating that crossinfection in groups of schoolchildren does not occur (Follett *et al.*, 1978).

Micromethods are being developed for HBV screening using finger prick blood samples on filter paper (Farzadegan *et al.*, 1978). Perhaps with the perfection of such methods, very large population studies may become feasible.

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Nathalie Masse

Nathalie Masse Research Fellowship. This is intended to help young workers engaged in research on problems in social and preventive paediatrics. It was granted for the first time in 1978 and will subsequently be granted in every even-numbered year. The next fellowship will be awarded in 1980, for which applications are invited by 31 December 1979.

International Nathalie Masse Prize. This prize of 10 000 French francs was created to reward original work concerning childhood, presented either by an institution or by an individual under 40 years, with a view to encouraging studies by young professionals and research workers. The prize will be awarded for the first time in 1979 (the list for this is now closed), and thereafter in every odd-numbered year. The next award will be in 1981 for which applications are invited by 1 September 1980.

All grant and prize winners will be chosen without regard to nationality by an international jury.

Details and application forms for the fellowship and prize are obtainable from the Memorial Committee, International Children's Centre, Château de Longchamp, Bois de Boulogne, 75016 Paris.

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Childhood cystinuria in New South Wales

Results in children who were followed up after being detected by urinary screening in infancy

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SUMMARY Homozygous cystinuria was diagnosed in 45 children and 19 of their siblings in the course of routine urine screening of 6-week-old infants in New South Wales. These children were followed for up to 14 years. During this time there were 5 clinical episodes of renal disease which could be ascribed to cystinuria. There was normal mental development in all the children except one. Of 49 children over 3 years, 4 had height centiles less than the midparent height centile, while 45 had height centiles equal to or above the midparent centiles. Family testing in these 45 cases showed that 60% were type I cystinurics, and 35% were of the mixed or compound type (5% were not classified). Data from the parents and grandparents showed that renal tract calculi had occurred in 14 of them. This study shows that children with homozygous cystinuria, detected by urinary screening in infancy, rarely have renal symptoms. Mental development was normal as was growth in height. There was an increased incidence of noncystine stone formation among the relatives of these children. The incidence of homozygous cystinuria in New South Wales is one in 17 286.

Cystinuria is a disorder of renal tubular and intestinal transport of amino-acids. the main clinical association being renal calculi formation. Colliss *et al.* (1963) reported a height deficit in cystinurics compared with the general population, and Scriver *et al.* (1970) suggested that mental retardation was an associated feature. Many cases of cystinuric stone formers have been described, mainly in adults, although in the study of Bostrom and Hambraeus (1964) in Sweden there were 9 children and adolescents, most of whom were identified by the clinical manifestations of calculus disease. We report the results in a group of children with homozygous cystinuria who were followed up after being identified by newborn screening of urine.

Methods

During a 13-year period (1964 to end of 1977), urine samples from 950 767 6-week-old babies in New South Wales, 85% of the infant population, were examined by unidimensional paper chromatography (Wilcken *et al.*, 1973). If this first urine test showed markedly raised levels of cystine, lysine, or arginine (ornithine is not well separated by this method) a repeat test was requested. These first two tests were performed on urine-soaked blotting paper slips, but if the second test also showed a gross aminoaciduria consisting of cystine, lysine, or arginine, a liquid urine specimen was requested. A definitive diagnosis of homozygous cystinuria was made if this test showed high levels of cystine, lysine, and arginine, the baby usually being 6 months by this stage.

Children with homozygous cystinuria were seen for initial assessment and then at least yearly. At each visit they were assessed clinically, their general health was assessed, and their parents were also questioned specifically about the occurrence of back ache, abdominal pains, renal pain or colic, haematuria, frequency of micturition, and scalding of urine. They were asked about any medication the child had received, the diet, and details of fluid intake. Height and weight (without shoes) of the affected children

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were measured as were also the heights and weights of the siblings and parents seen at the follow-up. No correction was made for parent's age, all being under 40 years of age. The children's height centiles and the midparent height centiles were calculated using the tables of Tanner *et al.* (1970). The parents were encouraged to bring the whole family to each visit and unaffected siblings were also seen several times in most families.

Formal IQ testing in these patients was not routinely done. Achievement of milestones was recorded and parents were asked to rate the development of the child as slower than, the same as, or quicker than that of unaffected siblings. Children who had completed at least 2 years of schooling were assessed by their school reports and their class level for the age. If they were in the top class for the age grade, they were rated as good, if in the middle class as average, and if in the lowest class they were rated as slow. Their school level was also compared with their siblings.

The management of the children was the same in all cases, namely increased fluids to the limit of tolerance. None of the children had been given urinary alkalinisers, D-penicillamine treatment, or protein restriction at the time of this report. Four children (from 2 families) were investigated biochemically on a number of occasions, but have not been seen by us. Information was obtained from the family doctor by means of a specific questionnaire, as described above.

At each follow up, a sterile midstream specimen of urine was obtained and this was immediately set up for microurine analysis by standard methods. Urinary amino-acids were examined at each visit by high voltage electrophoresis, cystine was estimated quantitatively (Rootwelt, 1967), the presence of excess arginine confirmed by the Sakaguchi reaction (Smith, 1969), and cystine crystals were sought using the method of Hepler (1950). These examinations were performed on fasting first morning urine specimens in most patients but in some of the older ones on a 24-hour urine specimen. In 4 cases, urinary amino-acids were estimated on a Beckman Unichrome amino-acid analyser.

Once the patient had reached age 4 or 5, a plain *x*-ray of the abdomen was taken to exclude the presence of a calculus, and this was repeated 2 or 3 years later in some of the older patients. A detailed genetic history was also obtained at the initial visit with specific questioning about family history of renal calculi, consanguinity, and abortions, as well as about more general genetic conditions. Urine specimens from both parents and all siblings were tested in each family; in some families other family members were also tested.

Results

Of 950 767 babies tested between the start of screening in 1964 and the end of 1977, 45 were found to have cystinuria, 19 of 89 siblings tested were also affected, giving a total of 64 known cases (Table 1). 38 were boys and 26 girls, giving a sex ratio of 0·59 ($P>0·2$). Ten of the 19 homozygous siblings were born after the propositus and are shown as propositi themselves in the incidence figures and in the discussion of initial urinary test findings. In one family 2 affected siblings of the propositus were unlike twins, and in another family with twins, one was homozygous and the other normal. The ages of the 64 children are shown in the Figure.

Initial urine testing showed a typical aminoaciduria

Table 1 *Siblings of the cystinuric propositi*

Propositi (n = 45)	*Siblings*			
	Homozygous	*Heterozygous**	*Normal*	*Total*
Boys (n=28)	19–10	18–11	52–33	89–54
Girls (n=17)	– 9	– 7	–19	–35

*From 16 mixed or compound families.

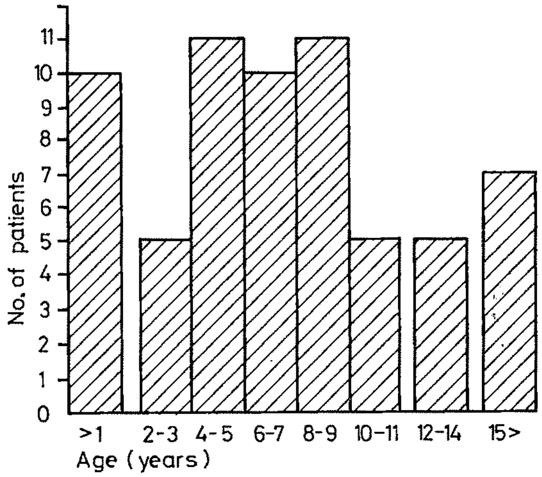

Figure *Age of 64 homozygous cystinuric patients. The scale for age ranges is not uniform, and changes in scale are shown by a space—for example the 12–14 block represents a 3-year period (1964–66), being years during which few cases were detected, and >1 block represents a one-year period (1977), a year in which there were many cases. The 7 patients, aged at least 15 years and born before 1964, were found when their families were tested. Two other siblings, older than the propositus (one 10, one 11 years), had not been screened in infancy and were also detected by family testing.*

at 6 weeks in 44 of 55 babies. In 11 patients, arginine was not detected in the first test, although the cystine and lysine levels were very high. Seven of these 11 patients showed the typical aminoaciduria in the second test; by this time the baby was usually 3 months. There were 4 boys in whom increased arginine excretion was not apparent at either of the first 2 blotting paper tests although cystine and lysine levels were very high; this was the indication for requesting a third test. Cystine, lysine, and arginine were all much increased in the subsequent liquid urine specimen in these children and have remained so.

Patients were definitively diagnosed at about 6 months, the 9 older siblings were diagnosed when family studies were undertaken. All were reviewed during the latter part of 1977 and first half of 1978. The age at last review ranged from 6 months to 22 years (oldest sibling) with mean age 7·6 years. 49 were at least 3 years and 28 were at least 8 years. Renal symptoms were present in 5 patients*. One boy had an episode of renal calculus formation at age 17½. One girl had episodes of right loin pain at 10½, and there were 2 cases of urinary tract infection, and a boy of 4 years had dysuria and a urinary tract infection; 4 months later a stone was detected on routine *x*-ray. There were also 3 children (2 boys, 1 girl) who were bed-wetters until about 9–10 years and there were 3 asymptomatic girls who showed urinary contamination, but not infection of urine, on routine microurine investigations at follow-up.

Routine *x*-rays of the abdomen had been performed in 42 of the children (in some of the older ones more than once) and in one case a calculus was seen which was asymptomatic. Routine tests for microscopic haematuria were negative in every patient at each follow-up.

The general health of the children was good and not significantly different from their siblings. There were 9 cases with noteworthy childhood conditions. One boy had a hemivertebra of L4 spine producing lumbar scoliosis; the adopted girl suffers from severe asthma requiring daily medication; one girl at 3½ years has grey carious irregular teeth; one boy aged 4 years had surgical correction of pyloric stenosis at 5 months; and one boy, free of renal symptoms, had a salivary gland calculus removed surgically at 7 years. Another boy aged 9 also had surgery for pyloric stenosis as a baby. One girl had mild minor retardation and attended the spastic centre until she was 5, and one boy had surgery for bilateral convergent strabismus. One further patient has petit mal epilepsy.

The growth of these homozygous cystinuric children appeared to be within the normal range. The mean birthweight was 3·07 kg (boys and girls combined) with a range of 1·76 kg (in a 7-week preterm girl) to 4·28 kg. In 5 babies the birthweight was low due to prematurity (including the twins), there were 2 term babies in whom the birthweight was low, but in all the others it was average. Birth length was not as consistently recorded as birthweight and was not known for 20 of the children, but in the remainder the mean birth length was 52·5 cm. Two children had birth lengths <3rd centile, the rest were between 10th and 90th centiles.

Height of the children at last follow up (of the 49 patients over 3 years) showed that 28 were on the same centile as their midparent height centile, 18 were above, and 4 were below this. Three of these children had unaffected siblings who were also below the midparent height centile, and the fourth, a 4-year-old boy, was on the 10th centile for height, the midparent height being on the 50th centile, but he was an only child and so had no siblings for growth comparisons. The heights of the parents of the adopted girl were not known, but she was on the 50th centile for height.

Results of genetic studies are shown in Table 2 using the genetic types as described by Rosenberg *et al.* (1966). In one case there were no family data as the patient had been adopted. In one family, the results of family testing could not be reconciled with current concepts of the genetic inheritance of cystinuria. Of the remaining 43 families, 27 were type I and 16 were of mixed genetic type, 6 in which both parents were carriers and 10 with one normal parent and one heterozygous parent.

The sex ratio among the siblings of the patients can be seen in Table 1 and is 0·5 for the homozygous siblings, 0·61 for the heterozygous siblings, and 0·64 for the normal siblings. Although there appear to be slightly more boys, particularly among the normal siblings, this was not significant (P>0·1). Data for sex ratio of newborn babies in N.S.W. were obtained from the Commonwealth Bureau of Statistics (Commonwealth Bureau of Statistics, 1978, personal communication).

There was no case of parental consanguinity in these families, nor was there any consanguinity

Table 2 *Genetic types in 45 families*

	No.	%
Type I	27	60
Type II–III	6	35·5
I–II/III	10	
Unknown*	1	2·25
Atypical†	1	2·25

*An adopted child, †Case 15.

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*Details of individual cases are available from authors on request.

known among either the maternal or paternal grandparents. One child was adopted, and this information was not known in this case. Among the siblings of the propositi, there were 13 early 1st trimester spontaneous abortions (in 9 of these families), 89 pregnancies proceeded to term. Given that 15% of all pregnancies abort, these findings indicate that there is no increased abortion rate among cystinuric heterozygotes. There were also 3 stillbirths and one case of premature labour of twins, neither of whom survived. Altogether, fetal loss in these families was not excessive.

Information about relatives with kidney stones was sought but it became clear during history taking that these data were inconsistent from family to family. Many relatives were reported to have had 'kidney trouble', but it was not always possible to verify the information. Only confirmed episodes of calculi among the parents and maternal or paternal grandparents are given, and hence this is a low estimate of the occurrence of renal calculi among relatives of the propositi. These data are shown in Table 3. These 14 relatives were tested and amino-acids were normal in 12 of them, where the calculi were clearly noncystine in composition. One paternal grandfather was a type II heterozygote cystinuric, and one maternal grandmother was a type III heterozygote. Stone analysis was not performed in either of these, but it would seem unlikely that the maternal grandmother had had cystine stones but possible that the paternal grandfather's stones contained cystine. In addition 2 of the fathers had each had a nephrectomy for congenital anomalies of the kidney.

Intellectual achievement of the patients was satisfactory. School progress is reported where at least 2 full years of schooling have been completed at last follow-up. This applied to 35 of the children, and of these, 14 were in the highest class for their age, 16 were in the middle for their age and considered average, and 5 were in the lowest class for their age. In this group of 5 slower children, one boy who was repeating his 3rd year of school was an only child, 2 boys had unaffected siblings considered to be average, one girl had 2 unaffected siblings also in the lowest class for their age, and one girl had an unaffected younger brother who had not yet started school. Of the 14 children in the highest class for their age, 3 were at the top and had excellent reports. One of these is the adopted girl, one girl was ahead of her two heterozygote siblings, and one boy, who had attended a special opportunity class for intelligent children in his area, was advanced compared with his homozygote brother and his 2 other unaffected siblings, who were all in the average class. Only 2 patients have completed their schooling, each was an elder sibling of a propositus. Both were average pupils at school, one is now an office worker and the other a student nurse.

The remaining 26 children include the babies, toddlers, preschool children and those who had not completed 2 full years of schooling. Developmental progress as assessed by milestones was entirely normal in 25 of these children. One child (Case 31) is mentally retarded in the mild to moderate range.

Table 3 *Relatives with renal calculi*

Relative	*No.*
Mother	1
Father	—
Paternal	
grandmother	1
grandfather	3*
Maternal	
grandmother	4
grandfather	5*
	14

*Two required nephrectomies; one was a heterozygote type II cystinuric, the propositus coming from a mixed family I–II/III.

Discussion

Cystinuria is a disorder of the transport of cystine and the dibasic amino-acids in both the renal tubule and the intestine. The presence of markedly high levels of cystine, lysine, and arginine in the urine of our patients, often with cystine crystalluria, clearly classified them as homozygotes. No intestinal absorption studies were undertaken. It is not always possible in the initial tests to distinguish homozygotes from heterozygotes. In 4 of our patients the classical aminoaciduria was not found in the first two screening tests and appeared in the third and subsequent test. A definitive diagnosis in these children was delayed until their third test had been performed. Similar problems were encountered by Levy *et al.* (1972) who also found repeat testing necessary in some cases; their urine screening programme was the most comparable to our own. The programme in Wales (Bradley, 1975) was similar in structure, but cystine was detected by the nitroprusside spot test initially. We found the nitroprusside test to be very accurate for detecting cystine in the urine, but false-positives and false-negatives may occur (Smith, 1977).

The incidence of cystinuria, based on routine screening of urine from normal infants, has recently been reported by Thalhammer (1975) as part of a collaborative study from 6 centres; Levy reported an incidence of one in 15 841 in Massachusetts, Thalhammer one in 1100 in Vienna, Hyanek in Prague found one in 22 065, Scriver in Montreal found one in 14 084, while in N.S.W. we reported an incidence of one in 5069. On reviewing our data, it was apparent that some cases of type II heterozygotes were included. With these cases eliminated and using an extended population sample, the incidence in N.S.W. has been reduced to one in 17 286. This figure is very similar to the incidence reported by Levy, but is still quite different from those found by Thalhammer (one in 1100), Hyanek (one in 22 065), and Bradley (1975) (one in 27 059 cases). These various figures may reflect true differences in the incidence of homozygous cystinuria throughout the world, or they may be the result of other methods used to detect cases or different criteria for the diagnosis of homozygous cystinuria.

Colliss *et al.* (1963) reported on the stature of 44 patients with cystinuria, 42 of whom had had renal calculus disease. The mean height, adjusted to the adult male population, was found to be 2·5 cm less than that of controls. Our data indicate that homozygous cystinuric children are not smaller than normal children. The height of the cystinuric children was below that expected using the midparent height centiles (Tanner *et al.*, 1970) in only 4 children, but 3 of these were nevertheless on the same height centiles as their unaffected siblings. In one case the propositus was an only child. The parents' heights were generally measured when the patients were seen, in some cases the father's height was reported by the mother.

The birth length data presented here, although incomplete, suggest that affected children do not begin life shorter than normal children. It may be that the shorter stature noted by Colliss is the result of renal calculus disease, as most of her patients had renal calculi; however, our 2 patients with calculi, a 17-year-old and a 4-year-old boy, were both on the 75th centile for height.

Scriver *et al.* (1970) suggested that defective brain transport mechanisms in cystinuric patients may lead to mental retardation. No patient in our group could be considered to be mentally retarded due to cystinuria. One boy was retarded but, as he had other handicaps and congenital deafness, it would not seem justifiable to consider that the retardation was due to cystinuria. Excluding this patient, the intellectual achievement of 35 children who had completed at least 2 years of schooling showed a wide scatter with only 5 being in the lowest class for their ages; they were, however, certainly not retarded. Of the remaining children, the milestones were all adequate and comparable with unaffected siblings, although 10 children born in 1977 were still too young to assess this accurately. Formal psychometry was not performed. Gold *et al.* (1977) did use psychometry on 26 patients in Canada and the intelligence levels of their patients were no different from those of their unaffected siblings or the normal population.

If mental retardation affects 1·5% of the population and the incidence of homozygous cystinuria is one in 15 000, then the chance of both conditions occurring coincidentally would be one in 1 000 000, or 5 people in N.S.W. As noted, only one such child was found.

The general health of these children was good and was in no way impaired by also having homozygous cystinuria. A possible exception is the finding of 2 cases of pyloric stenosis, but further studies will be required to prove if an association exists between the two conditions. Considering the number of patients and the length of time of follow up, there were very few renal symptoms. There were only 2 proved episodes of calculus formation, one episode of renal pain for which no cause was found, and 2 cases of urinary tract infection. This study suggests that renal symptoms in children with cystinuria are rare. The management of all these children consisted of increased fluid intake to the limit of tolerance. It would be satisfying to think that follow-up of the patients and encouragement to maintain increased fluids was the reason for lack of renal symptoms but, in fact, it was difficult to know in most cases what the child's fluid intake actually was, and fluid intake appeared to fluctuate from time to time. Without a control group and stringent control of fluid intake, this aspect of management cannot be adequately assessed.

Among this group of homozygote cystinurics, 60% of the informative cases were of type I inheritance, and 35% were mixed or compound types (Table 2). Bostrom and Hambraeus (1964), in their extensive survey of cystinuria in Sweden, showed that of 59 families studied, 10 contained demonstrable heterozygotes (which they called semicystinuria), giving 83% type I families. Out of 21 families studied by Harris and Warren (1953), 6 contained demonstrable heterozygotes, leaving 71% type I cystinurics (which they named completely recessive); Rosenberg *et al.* (1966) studied 15 patients and found 60% to be type I. The frequency of the different genetic types of cystinuria appears to vary with different populations, although in every large study, the completely recessive or type I form is the most common. This applies to all those studies where the propositi have been mainly stone-forming patients, and also to our study where the patients were detected in an unselected way by urinary screening. It appears, therefore, that the genetic type of the patient is not an important factor for cystine stone formation in a patient with homozygous cystinuria.

We found 14 relatives who had had renal calculi among 270 parents and grandparents (Table 3);

accurate figures for the incidence of renal calculi in this population are not available, but using the annual incidence of Malek (1977) of one in 1000 of the population in the USA, it does appear that our findings show an increase of noncystine stone formation among the relatives of cystinurics.

We thank Elizabeth McKenzie for help in compiling the data and Beryl Morris for typing the manuscript. The late Brian Turner first took an interest in urinary screening for cystinuria and encouraged us to continue follow-up of patients detected.

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Diagnostic considerations in ataxia-telangiectasia

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SUMMARY 13 children with ataxia-telangiectasia were followed for 6 years. Unlike previously reported cases, these patients had progressive, debilitating neurological disease and slight pulmonary or infectious symptoms. Immunological dysfunction was variable and endocrinological defects were absent. Oculomotor findings, α-fetoprotein levels, and the incidence of chromosomal breakage were the most consistent parameters in the diagnosis of the condition. This disease should be considered in any patient with chronic ataxia, regardless of immunological findings or whether he has a history of infections.

Boder and Sedgwick (1957) presented the first thorough review of ataxia-telangiectasia (A-T) and stressed the prevalence of sinopulmonary symptoms. The incidence of pulmonary complications was considered sufficiently significant to include them as part of the syndrome—ataxia, oculocutaneous telangiectasia, and recurrent sinopulmonary infections. Since then, reports have shown that sinopulmonary infections occur in 45 to 81% of cases (Boder and Sedgwick, 1958, 1963; Peterson *et al.*, 1964; McFarlin *et al.*, 1972; Polmar *et al.*, 1972). Search for the possible cause or causes of this increased incidence of infection in A-T led to a series of articles describing a variety of immunological abnormalities including lymphopenia, decreased lymphoid tissue (Eisen *et al.*, 1965), significant deficiency or absence of IgA (Fireman *et al.*, 1964; Eisen *et al.*, 1965; Epstein *et al.*, 1966; McFarlin *et al.*, 1972; Polmar *et al.*, 1972; Kiran *et al.*, 1974), IgE deficiency (Ammann *et al.*, 1969; McFarlin *et al.*, 1972; Polmar *et al.*, 1972), presence of low molecular weight IgM (McFarlin *et al.*, 1972), decreased delayed hypersensitivity reactions (Eisen *et al.*, 1965; Epstein *et al.*, 1966), decreased E-rosetting and PHA responses (McFarlin and Oppenheim, 1969; McFarlin *et al.*, 1972; Kiran *et al.*, 1974), and variable failure of thymic development (Peterson *et al.*, 1964; Eisen *et al.*, 1965; McFarlin *et al.*, 1972). Unfortunately, there has been no direct correlation between the incidence of any of these defects and the occurrence of sinopulmonary problems.

We were able to evaluate and follow up 13 patients with A-T. These patients differ significantly from those already described. The incidence of sinopulmonary infections was significantly lower and the extent of immunological defects much less severe. We describe the results of our evaluation and emphasise the heterogeneity of this disorder and the difficulties in diagnosis.

Materials and methods

Patients. All 13 patients were children seen at this hospital between 1972 and 1978. They were diagnosed as having A-T by meeting criteria of progressive cerebellar ataxia associated with eye movements simulating ophthalmoplegia, progressive oculocutaneous telangiectasia, and frequently, familial incidence. The population includes three sibships of two siblings in each.

Immunological testing

In vivo

Intradermal skin testing was done as previously described (Gelfand *et al.*, 1972), using *Candida albicans* extract, dermatophyton, diphtheria-tetanus, and streptokinase-streptodornase. A skin test was considered positive if >10 mm induration could be seen after 48 hours.

In vitro

Immunoelectrophoresis was carried out by microtechnique, and quantitative immunoglobulins by radial immunodiffusion. IgE levels were done by radioimmunoassay (Phadebas: Pharmacia, Montreal, Quebec). E-rosettes were determined by a modification of the method of Wybran *et al.* (1972).

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Lymphocyte transformation assays were performed as previously described (Gelfand *et al.*, 1972).

Nonimmunological testing. Autoantibodies were sought by indirect immunofluorescence to nuclear factors, DNA, mitochondria, smooth muscle, thyroid, and glomerular basement membrane.

α-Fetoprotein levels were carried out by Dr T. Waldmann, NIH, Bethesda, Md, using a radioimmunoassay technique (Waldmann and McIntire, 1972). Chromosome studies were done on peripheral blood lymphocytes.

Results

Clinical data. Table 1 shows that all patients had pronounced ataxia and oculocutaneous telangiectasia. Neurological symptoms were generally noted in the first 2 years of life, but in one patient these were first seen as late as 5 years. Disease was present in 3 sibships; parents were consanguineous in one case. Most significantly, sinopulmonary symptoms were absent or were slight in all 13 patients.

Antibody-mediated immunity (Table 2). Four out of 12 patients had a selective absence of IgA. Low molecular weight IgM was not detected on immunoelectrophoresis and absolute serum IgM levels were normal for age. IgE was present in normal amounts on repeated evaluation in all 11 patients tested. Functional evaluation showed a negative Schick test in 8/8 patients, indicating the presence of neutralising antibodies. One patient converted from a positive reaction after reimmunisation. Isohaemagglutinins were present in all patients. DPT-P booster injections were given to 7 patients, all of whom had significant increases in titres to these antigens.

Cell-mediated immunity (Table 3). Severe and persistent lymphopenia was present in one patient, moderate lymphopenia ($<1\cdot5 \times 10^9$/l lymphocytes) in 3 patients. Delayed hypersensitivity skin testing was positive to at least one antigen in 9/11 patients tested, equivocal in one (about 5 mm induration), and absent in one. E-rosettes were normal in 9/11 patients and slightly decreased in 2/11. PHA response was normal or only slightly decreased in 10/11 cases.

Nonimmunological data. One or more autoantibodies were weakly to strongly positive in 8/11 patients. Most significantly, α-fetoprotein levels were raised in

Table 1 *Clinical presentation*

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Ataxia*	4+	2+	+	3+	2+	4+	3+	3+	3+	2+	+	4+	+
Telangiectasia	+	+	+	+	+	+	+	+	+	+	+	+	
Sinopulmonary infections†	0	½+	1+	0	0	1+	0	0	0	0	1+	1+	0
Onset of symptoms (months)	12/12	9/12	15/12	14/12	13/12	14/12	14/12	24/12	10/12	60/12	12/12	12/12	14/12
Sex	F	M	M	F	M	M	M	F	F	F	M	M	M
Familial incidence	+ ←→ +			+ ←→ + (Parents consanguineous)		+ ←→ +							

*1+ mild ataxia, 4+ pronounced ataxia.

†0 ≤4 episodes of URI symptoms per year; ½+ >4 episodes of URI symptoms per year, not requiring medical care; 1+ recurrent clinical or radiological documentation of sinusitis and/or ≥4 URIs per year requiring outpatient visits; 2+ chronic sinusitis or 2–3 episodes of pneumonia; 3+ ≥4 episodes of pneumonia; 4+ bronchiectases.

Table 2 *Immunological data*

B-cell function	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
IgG (mg/100ml)	1880	2000	800	570	900	940	445	850	800	1000	1081	800
IgA (mg/100ml)	0	0	40	50	0	130	150	115	70	0	125	180
IgM (mg/100ml)	260	480	200	300	86	225	200	190	150	175	200	222
IgE (ng/ml)	200	460	520	100	98	248	248	160	228	79	53	ND
Schick test†	–	–	ND	–	ND	–	–	–	ND	+ → – With boost	–	ND
Isohaemagglutinins												
Anti A:			1:32	1:32	1:256	1:128	1:64					
Anti B:	1:256	1:128	1:256	1:128	1:4	1:128	1:64	1:16	1:16	ND	1:32	ND
Blood type	(A+)	(A+)	(0+)	(0+)	(0+)	(0+)	(0+)	(A+)	(A+)		(A+)	

†Positive skin test to diphtheria toxin, indicating absence of neutralising antibody; – no reaction indicating presence of antibodies.
ND = not determined.

Table 3 *Immunological data*

T-cell function	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Lymphocyte count (× 10^9/l)	1·0	1·5	2·0	1·2	1·7	1·5	1·0	4·0	1·8	0·5	3·5
Delayed hypersensitivity	+	±**	+	+	+	+	+	+	+	+	−
E—rosettes†	N	N	N→↓	N	↓	N	N	N	N	N	N
PHA‡	N→↓	N→↓	N	N	N	N	N→↓	N	N	N→↓	↓↓

**This patient had a response to Candida, with 5 mm of erythema and induration.

† % E-rosettes was considered decreased (↓) if percentages were within 1 SD of the mean for controls. (Laboratory controls for E-rosettes ranged from 50–65 % of peripheral blood mononuclear cells with a mean of 55.)

‡PHA responses were considered to be decreased to within 1 SD (↓) or 2 SD (↓↓) from the mean of control values (the mean control value was 33000 counts/min).

N = normal.

Table 4 *Nonimmunological data*

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Autoantibodies	+	+	+	+	+	+	−	−	−	+	+	ND
Liver function tests†	N	N	N	N	N	N	N	N	N	N	N	N
α-Fetoprotein‡	250	300	180	255	100	240	310	160	280	94	44	ND
Glucose tolerance	N	N	N	ND	ND	N	N	N	ND	ND	N	ND

†AST, bilirubin, alkaline, phosphatase; ‡normal range ≤40 ng/ml.

Table 5 *Chromosomal abnormalities*

	1	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
No. of cells examined	56	6	52	50	50	50	32	53	39
No. of cells with breaks	35	2	6	6	6	4	5	3	2
% cells with breaks†	62	33	11	12	12	8	16	6	5
D-group affected (13–15)	+	+	+	+	+	+	−	−	+
Chromosome—14 affected	−	−	+	−	+	+	−	−	+
Chromosome—7 affected	+	+	−	−	−	−	−	−	−
Clones	+	−	+	+	−	−	−	−	−

†Normal = <6% of cells with breaks.

11/11 cases. In one patient the level (44 ng/ml) was just outside the normal range (Waldmann and McIntire, 1972) (Table 4).

Chromosome breakage was present in 8/9 cases. Chromosome-7 was affected in 2 patients and chromosome-14 in 4. D-group involvement was present in 7 patients. Clonal expansion of aberrant chromosomes was noted in 3 cases (Table 5).

So far malignancy has occurred in only one patient (Case 6), who developed acute lymphoblastic leukaemia. Prolonged glucose tolerance tests were normal in all 7 patients tested. Electrolytes, thyroid function studies, and pituitary hormone levels (FSH, LH, growth hormone) were also normal in these patients.

Discussion

Since the complex of progressive cerebellar ataxia associated with bulboconjunctival telangiectasia was first reported in 1926, the multisystem nature of this disease has become clearer (Peterson *et al.*, 1964; Ammann *et al.*, 1970; Paterson *et al.*, 1976). It is now known that involvement may include hepatic and endocrine organs, as well as neurological and immunological systems. The presence of debilitating sinopulmonary disease has been reported as a significant element of this syndrome (Boder and Sedgwick, 1957, 1958, 1963; Peterson *et al.*, 1964; McFarlin *et al.*, 1972). Correlations between pulmonary dysfunction and immunological abnormalities have been looked for without success (Boder and Sedgwick, 1963; Peterson *et al.*, 1964; Eisen *et al.*, 1965; Rosenthal *et al.*, 1965; Ammann *et al.*, 1969, McFarlin *et al.*, 1972).

Our patient population was distinctly different from those reported in the past in that the incidence of sinopulmonary disease was virtually nil. Several possible reasons for this difference may be considered. Firstly, it is possible that we have a genetically isolated population differing from others with this disease. This is unlikely, as our patients came from varied ethnic groups and from different parts of Canada. The second and most likely possibility is that with increased awareness of this disease entity, less severe cases of A-T are now being diagnosed.

Immunological evaluation of our patients has shown similarly minimal dysfunction. IgA deficiency was present in 4/12 (33%) patients, a figure somewhat below those previously reported (Fireman *et al.*, 1964; Eisen *et al.*, 1965; Ammann *et al.*, 1969; McFarlin *et al.*, 1972; Polmar *et al.*, 1972; Kiran *et al.*, 1974). Interestingly, in one of our families, IgA deficiency was present in one patient and not the other, suggesting that the defect in this disease may not reflect a single gene phenomenon, or at least all deficits are not expressed in a simple recessive genetic fashion. IgE levels were found to be within the normal range in all patients. This is at variance with other reports of A-T (Epstein *et al.*, 1966; McFarlin *et al.*, 1972; Polmar *et al.*, 1972). Overall antibody function appeared to be adequate in these patients, as shown by a negative response to the Schick test, the presence of isohaemagglutinins, and a normal booster response to antigen challenge. Similarly, T-cell function was grossly intact in these patients as suggested by delayed-hypersensitivity reactivity, E-rosette formation, and mitogen-induced lymphocyte proliferation. Significant lymphopenia was observed in only one patient. We could find no correlation between an immune defect and sinopulmonary disease in our patients. Specifically, the 4 patients with most noticeable pulmonary symptoms had normal IgA and IgE levels, and lymphocyte counts. Delayed hypersensitivity reactions were absent in one of these patients, percentages of E-rosette forming T-cells were normal or only slightly decreased in all 4. The PHA response was within 1 SD of the mean for normal controls for 3 of these 4 individuals.

Levels of α-fetoprotein were raised in all these patients. This finding, first reported by Waldmann and McIntire (1972), may well become an invaluable diagnostic tool when the diagnosis of A-T is uncertain. Chromosome breakage was extensive in these patients, being present in 8/9 of our patients in whom an adequate number of cells could be obtained for examination. These breaks were of no specific type or unique pattern, although as in other reports (Cohen *et al.*, 1973; Hecht *et al.*, 1973; Nelson *et al.*, 1975), there was a high incidence of group-D involvement.

These findings suggest that the diagnosis of A-T should be considered in patients with moderate to severe neurological symptoms and less obvious involvement of cutaneous or pulmonary systems. We have found the pseudo-ophthalmoplegia in these patients a consistent finding and a useful aid in the diagnosis. α-Fetoprotein levels and evaluation for chromosome breakage have also proved to be valuable diagnostic aids in evaluating equivocal cases of this syndrome. With further awareness of the full range of expression of A-T, more cases without a history of infections and with normal immunological findings will be recognised.

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Exchange transfusion in newborn infants: effects on granulocyte function

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SUMMARY During 23 exchange transfusions, the granulocytes from 27 donors and 16 newborn infants were tested for opsonic activity and granulocyte function by the nitrobluetetrazolium test. Granulocyte function in a newborn baby receiving an exchange transfusion can be altered positively or negatively, depending on the quality of the donor's blood. If exchange transfusion is used in the management of neonatal sepsis, special attention should be given to the immunological properties of the donor blood.

Studies have shown the sometimes strikingly beneficial results from blood exchange transfusion (ET) in neonatal septicaemia with sclerema (Prod'hom *et al.*, 1974; Torrado *et al.*, 1974; Xanthou *et al.*, 1975). These results have been attributed to various mechanisms—such as the mobilisation of bone marrow leucocytes (Xanthou *et al.*, 1973), or a rise in serum opsonic activity (Davis *et al.*, 1971). We tested granulocyte function by the nitrobluetetrazolium (NBT) test (Rubinstein and Pelet, 1973), and opsonic activity (Soothill and Harvey, 1976), before, during, and immediately after ET.

Table *Granulocyte function in 16 infants given exchange transfusions*

Case	*Gestational age (weeks)*	*Birthweight (g)*	*Diseases*	*Age at ET (hours)*	*Neutrophils × 10⁹/l*	*Bands/ segmented neutrophils*	*Opsonisation index*	*NBT after maximum stimulation*
1a	31 (Small-for-dates)	1160	*Escherichia coli* septicaemia and meningitis, sclerema (and death)	20	1·3	6·6	3·8	—
b				27	3·8	2·5	3·7	—
c				81	4·7	0·8	4·2	—
2a	36	2100	*E. coli* septicaemia, sclerema	35	0·5	2·1	1·4	96
b				49			3·9	92
c				61	1·4	0·9	3·2	95
d				72	2·4	1·4	4·5	68
3a	32	1710	Sclerema	36	3·4	3·0	2·0	52
b				125	4·5	0·4	4·4	24
4	40	2760	*Staphylococcus aureus* septicaemia	60	1·5	2·1	6·2	98
5	33	2430	IS, neonatal asphyxia, HMD	20	2·3	1·3	1·95	96
6	33	1740	IS, HMD	60	3·0	0·6	5·0	93
7	33	1560	IS, HMD	49	1·2	1·4	6·3	80
8a	37	2910	IS, Rh incompatibility	12	9·7	1·1	2·5	96
b				38	6·2	0·5	1·1	94
9	41	3480	Rh incompatibility	46	9·0	0·3	4·5	69
10	40	3950	Rh incompatibility	72	7·8	0·1	2·1	20
11	36 (Small-for-dates)	2000	ABO incompatibility	10	14·6	0·3	2·4	82
12	40	3490	ABO incompatibility	58	12·8	0·1	4·6	93
13	40	3300	Hyperbilirubinaemia of unknown origin	78	3·4	0·03	6·4	92
14	40	2820	Hyperbilirubinaemia of unknown origin	120	2·6	0·2	5·7	93
15	40	2830	Hyperbilirubinaemia of unknown origin	111	4·3	0·06	5·7	96
16	40	3200	Hyperbilirubinaemia of unknown origin	85	5·6	0·1	1·6	98

IS = Infective syndrome, newborns with clinical features suggesting infection, but no infection documented, HMD = hyaline membrane disease.

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Patients and methods

16 preterm and term babies had 23 ETs with 180 ml/kg fresh (<60 hours old) citrated blood (Table). In all of the severely ill newborn babies (Cases 1–8), ET followed earlier transfusions and was combined with chemotherapy (gentamicin, ampicillin, and cloxacillin). Blood samples were obtained from the donor before ET, and then from the baby at the beginning, at one-third and at two-thirds of the ET volume, and at the end of ET.

Leucocytes were isolated from heparinised blood on a Dextran 500 (Urografin) density gradient according to Böyum (1968). NBT reduction was tested, as previously described (Rubinstein and Pelet, 1973), for spontaneous and maximum capacity after stimulation with antigen-antibody complexes (normal human serum and sheep antitotal human serum, Behring). The opsonisation index was determined for the infant's and the donor's serum (2·5%), using the method of Soothill and Harvey (1976). Leucocytes were incubated in the presence of serum with yeast particles for 30 minutes at 37°C. After low-speed centrifugation, one drop of the pellet was dried on a slide and stained with May-Grünewald-Giemsa. The greatest number of yeast particles per granulocytes was 8. As the aim of this study was to find out the effect of ET on granulocyte function, each newborn baby was classified according to the degree of his granulocytic dysfunction and that of the donor.

Statistical analysis used Student's *t* test.

Results

Opsonisation index. This was 4·88 ± 0·26 in 25 of the 27 donors. In the remaining 2 donors (Cases 7 and 9) it was extremely low (<1) and only in ET with blood from them was there a decline in the opsonic activity of the baby's blood (from 6·3 and 4·5, to 0·7 and 1·7). In 15 ETs the index was initially similar in blood from the donor and patient and no change occurred after ET (4·56 ± 0·31, to 4·62 ± 0·31). In 5 ETs in 5 patients (Cases 2a, 3a, 5, 8b, 16) a low opsonisation index was improved by ET with donor blood of a normal index (Fig. 1).

Granulocytes from 9 patients were tested for uptake of yeast particles in autologous and donor sera (Fig. 2). In 11 ETs both sera gave identical results. In 4 ETs in 4 children (Cases 2a, 3a, 8b, 16) there was a significantly lower opsonisation index when the infant's leucocytes were tested in autologous serum compared with donor's serum. This difference disappeared during ET. In 2 patients a lower opsonisation index was observed in the donor's

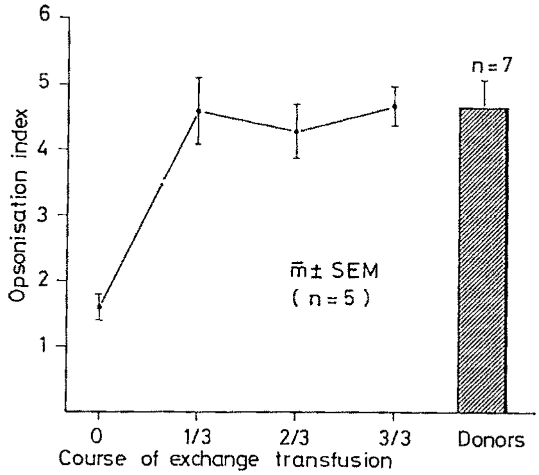

Fig. 1 *Opsonisation test; infants deficient for yeast opsonisation transfused with donor blood with normal yeast opsonisation.*

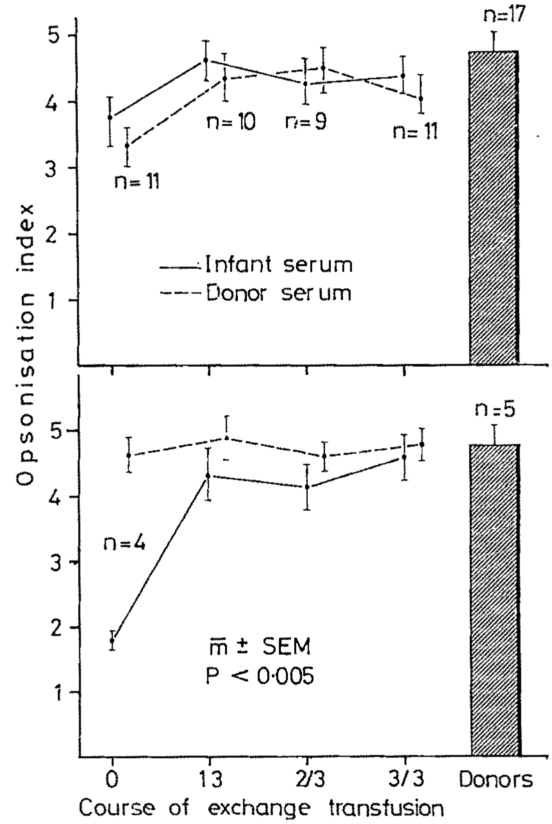

Fig. 2 *Opsonisation test performed on the sera from the baby and donor.*

serum compared with autologous serum. This, however, did not affect the opsonisation index after ET.

Spontaneous NBT reductive activity. Granulocytes showed a wide scatter, as was reported by Moro (1976). In one patient (Case 2) with septicaemia and sclerema, an initial ET with blood containing granulocytes with a low maximum NBT reductive capacity caused no change in the infant's granulocyte spontaneous reduction, while ET with granulocytes of a high maximum NBT reductive capacity improved the infant's granulocyte spontaneous function (Fig. 3).

Maximum NBT reductive capacity. Granulocytes were tested in donor blood and in every baby except one (Case 1). Granulocytes from 13 (52%) donors exhibited normal values (89 ± 2·6%), 8 (32%) donors had moderately decreased values (66 ± 5·6%), and 3 (16%) donors had a much depressed NBT reductive capacity (26 ± 6%). If the donor's granulocytes were normal or slightly depressed for this parameter, no change in the NBT reductive capacity was detected in the infant's blood (Fig. 4). In 3 children with normal maximum reductive activity (Cases 2a, 6, 7), ET with granulocytes of low maximum NBT reductive capacity resulted in a decrease for this parameter in infant's blood obtained at the end of ET. Three babies (4 ETs) (Cases 2e, 3a, 3b, 10) who initially had very depressed NBT reductive capacities received granulocytes with normal reductive capacities and by the end of the ETs, the NBT reductive capacity was normal in all 3 patients (Fig. 5).

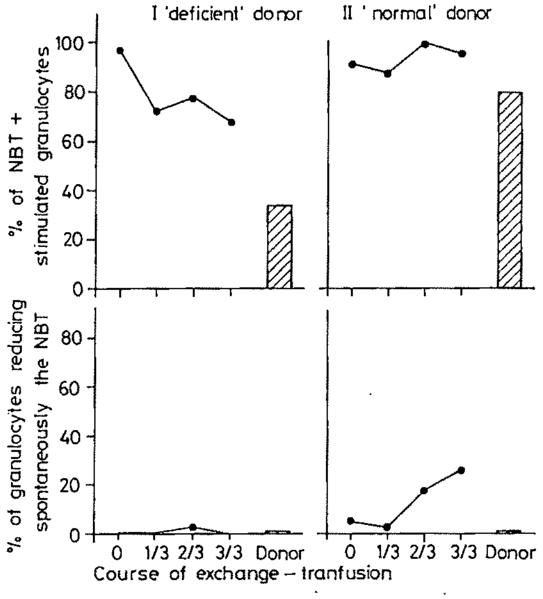

Fig. 3 *(Cases 2a and b) Infants' granulocyte spontaneous and maximum reductive capacity of NBT during exchange transfusion; a preterm baby with* Escherichia coli *septicaemia and sclerema receiving initially a 'deficient', then a 'normal' donor.*

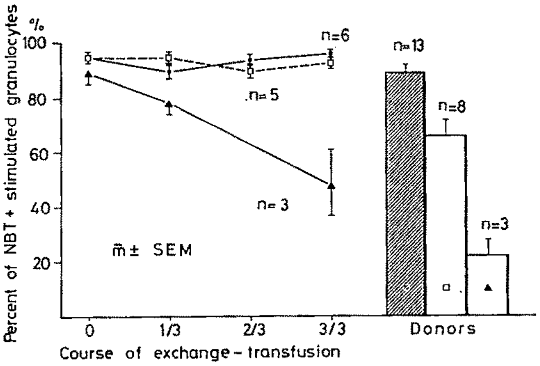

Fig. 4 *NBT test; 'normal' infants transfused with 'normal' or 'deficient' donors.*

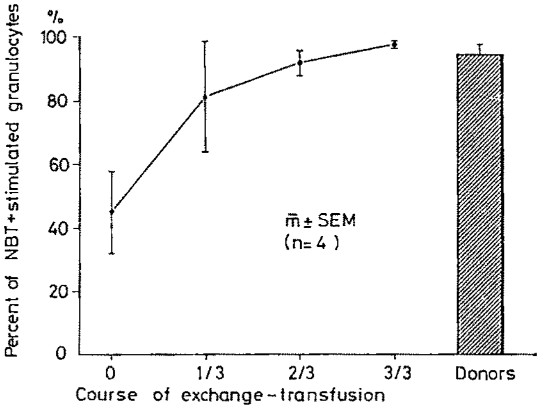

Fig. 5 *NBT test; 'deficient' infants transfused with 'normal' donors.*

Discussion

Our aim was to determine the effects of exchange transfusion on the opsonic activity and granulocyte function of the newborn. Many abnormal immunological functions have been reported in healthy term and preterm babies, including decreased serum opsonic activity, low granulocyte NBT reductive capacity, and altered cell membrane stability (McCracken and Eichenwald, 1971; Stossel *et al.*, 1973; Miller, 1975). But, as suggested by Soothill and

Harvey (1976), we should consider the possibility that decreased opsonisation may be a congenital deficiency. Although the family of neither the baby nor the donor was studied, nor were 'deficient' recipients or donors further studied, an 18-months' follow-up of all newborns affected by septicaemia or other infective illnesses, led to no instance in which such congenital deficiency was suspected.

These data indicate that ET may improve such *in vitro* functions and may possibly modify the poor prognosis of infected infants. We have shown that donor ET blood with normal opsonisation for yeast, and/or donor granulocytes with normal maximum NBT reductive capacity, tended to improve the corresponding function in the newborn baby's circulation. On the other hand, the use of donor blood which was deficient in these functions impaired the opsonic activity and/or the NBT reductive capacity of the recipient. Theoretically, the decrease in opsonins after ET could be due to the dilution of patient's serum with donor serum of low opsonic activity. The effects of ET on granulocyte function may be related to a different mechanism, since transfused granulocytes generally rapidly disappear from the circulation of the recipient, possibly due to clearance (in a positive case) or transfusion (in a negative one) of an inhibitor. It is possible, however, that their retention in the circulation of the newborn is prolonged.

If ET is used in the management of neonatal sepsis, special attention must be given to the immunological properties of such blood. The transfusion of blood with inadequate opsonic activity may prove to be detrimental as judged by a consequential diminution in the recipient's circulation.

A surprising finding was that half the samples of donor blood exhibited an abnormal opsonic and/or NBT reductive capacity of polymorphonuclear leucocytes. The most likely cause is that blood had been stored and then been incorrectly handled (McCullough *et al.*, 1974). As it is impracticable to screen every blood sample for its granulocyte and opsonic function, fresh blood which has been stored at 4°C for no longer than 12 hours should be used.

The clinical importance of correcting these immunological functions by means of ET has yet to be determined on a larger scale. Our initial studies show that the course of neonatal sepsis with sclerema neonatorum may be altered by ET.

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Familial hypobetalipoproteinaemia in 9 children diagnosed as the result of cord blood screening for hypolipoproteinaemia in 10 000 Danish newborns

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SUMMARY Out of 10 440 children, 266 with low (<2·5 centile) values for very low-low density lipoproteins in cord serum were chosen to be followed up to find out how many came from families with familial hypobetalipoproteinaemia (FHBL). In 176 families (66% of 266 families), FHBL was diagnosed in 9 children and their families.

Familial hypobetalipoproteinaemia (FHBL) is a genetic disorder which differs from classical abetalipoproteinaemia (ABL) by the presence in the serum of abnormally low, immunochemically identifiable, low density lipoproteins (LDL) in the propositus and in at least one first-degree relative (with no disease to which hypobetalipoproteinaemia could be secondary). An autosomal dominant mode of inheritance is likely (Herbert *et al.*, 1978). FHBL has been described in homozygous and heterzygous forms (Cottrill *et al.*, 1974). Homozygotes are biochemically indistinguishable from patients with ABL having no apolipoprotein B (apo B) or LDL, but they lack the severe neuromuscular degeneration typical of ABL (Salt *et al.*, 1960; Cottrill *et al.*, 1974; Biemer and McCammon, 1975; Muller and Lloyd, 1977; Herbert *et al.*, 1978).

The heterozygous condition is normally asymptomatic; there are however data which suggest that the low serum LDL-C levels may defer the development of coronary heart disease (CHD), thus prolonging life expectancy (Glueck *et al.*, 1976a). This makes FHBL of interest in regard to CHD prevention. So far only two children have been reported born with low levels of total cholesterol (T-C) and LDL-C who were found to have FHBL (Glueck *et al.*, 1976b; Stein, 1977). We describe 9 more such children.

Patients

In our screening programme for hyper- and hypolipoproteinaemia, cord blood was obtained from 10 440 infants (Andersen and Gry Nielsen, 1976). 266 (2·5%) of the 10 440 infants with the lowest VLDL-LDL values were chosen to find out whether they came from families with FHBL.

176 (66%) of the 266 families joined the study after informed consent. Venous blood samples were taken from all 176 fathers and 176 mothers after a 12-hour fast and at least 3 months after birth of their children. Serum lipid and lipoprotein values were determined for each, and if serum T-C was found to be below the sex- and age-adjusted 5th centile value for normal Danes (Andersen and Friis-Hansen, 1976), they were estimated at least three times more, and all other members of the family were invited to join the study so that their serum lipids and lipoproteins could also be determined. In the children <2 years venous blood was taken after an 8-hour fast, in the children >2 years it was taken after a 10- to 12-hour fast.

Methods

Cord serum VLDL-LDL was measured by a modification of the $CaCl_2$-heparin turbidimetric method

Abbreviations:

FHBL:	Familial hypobetalipoproteinaemia
ABL:	Abetalipoproteinaemia
apo B:	Apolipoprotein B
CHD:	Coronary heart disease
T-C:	Total cholesterol
TG:	Triglyceride
VLDL:	Very low density lipoproteins
LDL:	Low density lipoproteins
HDL:	High density lipoproteins

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of Burstein and Samaille (1959), on a Greiner Selective Analyser II using 20 µl serum and 1000 µl $CaCl_2$-heparin-precipitation solution. After 5 minutes at 37°C the sample was read at 578 nm against a sample blank. Concentration of VLDL-LDL was expressed in arbitrary units corresponding to the extinction. A frozen (−20°C) stock solution of pooled cord serum (VLDL-LDL concentration: 45 arbitrary units) was thawed and included in over 100 runs. Coefficient of variation was 1·6%, T-C was measured enzymatically on a Greiner Selective Analyser II as described by Borner and Klose (1977). Two cholesterol standards (K-77 and Pathonorm) were included in over 250 separate runs; coefficients of variation were 3·1 and 4·0% respectively. VLDL-LDL-C was measured manually after $CaCl_2$-heparin-precipitation in duplicate (Andersen and Gry Nielsen, 1976). VLDL-C was measured manually in duplicate after ultracentrifugation in a 40·3 rotor, Beckman type L ultracentrifuge at 10°C at 40 000 rev/min for 20 hours. Tubes were sliced. HDL-C values were calculated as the difference between T-C and VLDL-LDL-C.

Serum TG was measured manually in duplicate using the enzymatic method of Eggstein and Kreutz (1966). Two Liponorm triglyceride standards were included in over 100 separate runs. Coefficient of variation was 3·6% (for the 0·42 mmol/l triglyceride Liponorm) and 2·0% (for the 2·50 mmol/l triglyceride Liponorm). Nonparametric statistics (Siegel, 1956) were used.

Results

The serum lipid and lipoprotein values were analysed in the first 200 parents who joined the study. Eight of these 200 parents had serum T-C below the sex- and age-adjusted 5th centile value for normal Danes (Andersen and Friis-Hansen, 1976) and so were assessed for FHBL. Serum lipid- and lipoprotein values in the remaining 192 parents and their 17 children aged 5–19 years are given in Table 1.

Table 1 *Centile values for T-C and LDL-C in the reference groups*

Age groups (years)	*n*	*Centile values*									
		5		*10*		*50*		*90*		*95*	
		T-C (mmol/l)	*LDL-C (mmol/l)*	*T-C (mmol/l)*	*LDL-C (mmol/l)*	*T-C (mmol/l)*	*LDL-C (mmol/l)*	*T-C (mmol/l)*	*LDL-C (mmol/l)*	*T-C (mmol/l)*	*LDL-C (mmol/l)*
1–2	190	3·48	1·58	3·69	1·83	4·75	2·61	5·77	3·42	6·08	3·67
3–4	64	3·40	1·51	3·69	1·92	4·72	2·47	5·75	3·43	6·07	3·82
5–19	17			3·89	1·50	4·30	2·09	5·56	3·02		
20–29											
Women	64	4·31	1·82	4·41	1·96	5·20	2·64	6·62	3·91	7·07	4·14
Men	52	4·22	1·85	4·33	2·12	5·13	2·64	6·57	3·70	6·72	4·07
30–39											
Women	33	4·57	2·04	4·64	2·23	5·38	2·81	6·30	3·90	6·94	4·76
Men	43	4·46	2·14	4·70	2·33	5·46	2·99	6·73	3·95	6·88	4·15

Conversion: SI to traditional units—cholesterol: 1 mmol/l ≈ 38·6 mg/100ml..

Table 2 *Lipid and lipoprotein-cholesterol values in parent/child pairs with familial hypobetalipoproteinaemia*

Kindred	*Age (years)*	*T-C (mmol/l)*	*VLDL-C (mmol/l)*	*LDL-C (mmol/l)*	*HDL-C (mmol/l)*	*TG (mmol/l)*
1 III 4	28	3·56	0·12	0·96	2·48	0·42
1 IV 4	1·4	3·16	0·09	0·81	2·26	0·39
2 III 2	26	4·03	0·11	1·28	2·64	0·40
2 IV 1	2·3	3·34	0·58	0·95	1·81	1·34
3 IV 2	32	4·09	0·09	0·97	3·03	0·42
3 V 2	1·1	2·94	0·08	0·73	2·13	0·49
4 III 2	26	3·68	0·06	0·99	2·63	0·49
4 IV 1	1	2·10	0·27	0·49	1·34	0·44
5 III 7	29	3·82	0·47	1·93	1·42	1·17
5 IV 5	1·3	2·76	0·08	1·24	1·44	0·62
6 III 1	32	3·58	0·13	1·10	2·35	0·55
6 IV 3	2	3·25	0·40	1·03	1·82	1·04
7 III 2	24	4·01	0·15	1·31	2·55	0·58
7 IV 1	1·1	2·54	0·36	0·68	1·50	0·76
8 III 4	19	3·97	0·09	1·36	2·52	0·39
8 IV 1	1·3	3·31	0·04	1·13	2·14	0·39
9 II 1	46	3·47	0·47	1·75	1·25	1·23
9 III 10	1·6	3·37	0·20	1·33	1·84	0·89

Conversion: SI to traditional units—triglyceride: 1 mmol/l ≈ 88·5 mg/100 ml.

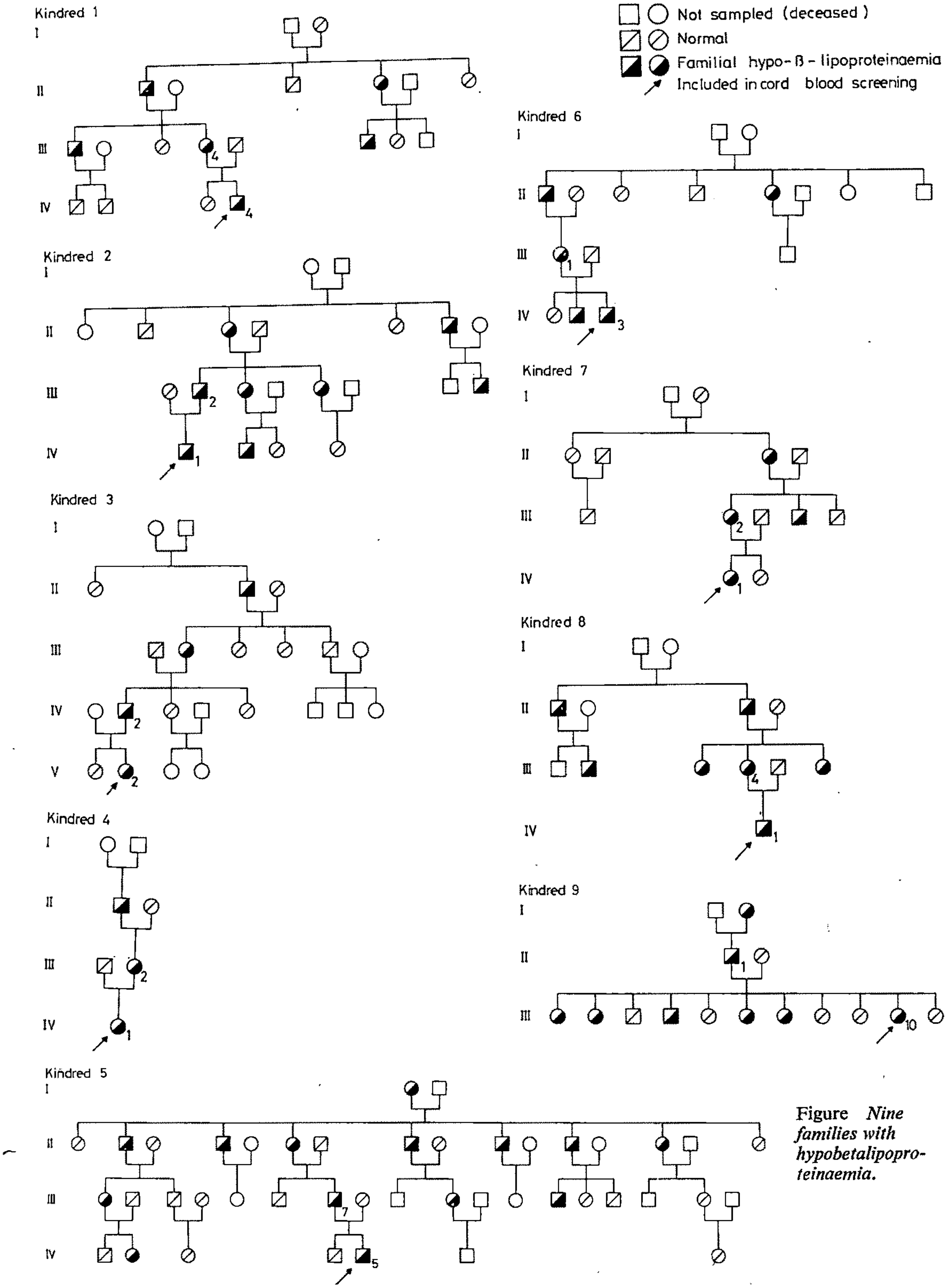

Figure *Nine families with hypobetalipoproteinaemia.*

Table 1 also gives the serum lipid- and lipoprotein values in 190 children aged 1–2 years described by Andersen *et al.* (1979a), and in 64 children aged 3–4 years described by Andersen *et al.* (1979b).

FHBL was found in 9 of the 176 families followed up. These 9 families are shown in the Figure, and the corresponding lipid- and lipoprotein values in parent/child pairs are given in Table 2. None of the parents or grandparents had been known to have FHBL before the study.

Discussion

The distribution of serum T-C values in 20- to 29- and 30- to 39-year-old men and women in the study is almost identical with that found earlier in similarly aged Danish fathers and mothers, in whom the 5th centile value for serum T-C was 4·26 and 4·42 mmol/l respectively (Andersen and Friis-Hansen, 1976).

The study did not allow precise calculation of the incidence of FHBL in Danish children, as only 66% of newborn babies with <2·5 centile values for cord serum VLDL-LDL were studied. As out of 10 000 consecutively born infants we found 9 with a three-generation vertical transmission of hypocholesterolaemia, this gives an incidence of at least 0·09%.

Hitherto only two children with FHBL had been reported with low cord serum T-C and/or LDL-C. The child described by Glueck *et al.* (1976b) had a normal cord serum T-C of 1·37 mmol/l and a low LDL-C of 0·23 mmol/l. In the child described by Stein (1977) cord serum T-C was 1·29 mmol/l and LDL-C 0·44 mmol/l. In the present study where only the cord serum VLDL-LDL was determined by the turbidimetric screening method, we show that in newborn babies with low values of cord serum VLDL-LDL, FHBL can be diagnosed at follow-up in at least 0·09% of the children and their families. The condition is therefore by no means a rare inborn error of metabolism.

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Lipoprotein measurements—a necessity for precise assessment of risk in children from high-risk families

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SUMMARY Serum lipids and lipoproteins were measured in 67 high-risk children, aged between 2 and 17 years, who were the offspring of 33 fathers with hypercholesterolaemia. 18 of the 33 fathers had had a myocardial infarction (MI) before 44 years of age. In 15 of the fathers there was no history of accelerated coronary heart disease (CHD). No difference in the concentrations of the serum lipids and lipoproteins was found between the children whose fathers had a history of MI (n = 31) and the children with no family history of CHD (n = 36). Serum lipids and lipoproteins were also measured in a control group of 19 children, aged between 2 and 17, whose parents were normolipaemic and had no history of atherosclerosis. Serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDLc) concentrations were significantly higher—5·47 ± 1·36 mmol/l (211 ± 52 mg/100 ml) and 3·55 ± 1·16 mmol/l (137 ± 45 mg/100 ml) respectively—in the 67 'high-risk' children than in the control group—TC, 4·46 ± 0·64 mmol/l (172 ± 25 mg/100 ml); LDLc, 2·56 ± 0·64 mmol/l (99 ± 25 mg/100 ml). No statistically significant difference was found in serum triglyceride (TG) or high-density lipoprotein-cholesterol (HDLc) concentrations between these two groups.

In 7 of the high-risk children, raised levels of serum TC >5·74 mmol/l (>221 mg/100 ml) were due to raised HDLc >1·95 mmol/l (>75 mg/100 ml) and normal LDLc <3·84 mmol/l (<148 mg/100 ml). In spite of their increased TC levels these children are probably at a lower risk for CHD as a result of the protective effect of HDL. In 3 children, raised concentrations of LDLc (>3·84 mmol/l) were accompanied by low levels of HDLc (<1·19 mmol/l) and normal concentrations of TC (<5·74 mmol/l). These children are probably at the highest risk for CHD.

The correct diagnosis would have been missed in 10 (15%) of the children had only TC been measured. It is therefore imperative to measure lipoprotein levels in addition to TC in all children from 'high-risk' families, regardless of their TC concentrations.

During the last two decades some risk factors associated with coronary heart disease (CHD) in young adults have been identified. Ways have been found to reduce these risks as a possible means to prevent, or at least delay, CHD (Berenson *et al.*, 1978; Glueck *et al.*, 1978a, b). As many of these risk factors can be identified in childhood, attempts to change relevant behaviour—for example, diet, physical activity, and smoking—may usefully be made at this age.

In adults there is a positive association between CHD and serum total cholesterol (TC) and low-density lipoprotein (LDL) (Kannel *et al.*, 1971; Tyroler *et al.*, 1975; Castelli *et al.*, 1977). More recently, an inverse association between high-density lipoprotein (HDL) and CHD has been established (Tyroler *et al.*, 1975; Glueck *et al.*, 1976; Castelli *et al.*, 1977).

Of the known risk factors for CHD, plasma lipids and lipoproteins are particularly relevant to children because (1) hypercholesterolaemia can be detected at an early age, and (2) dietary modification, combined in severe cases with cholestyramine, can lower the levels of serum cholesterol in children (Segall *et al.*, 1970; West and Lloyd, 1973; Glueck *et al.*, 1978b).

Although screening large groups of children to detect familial hypercholesterolaemia (FH) is unlikely to be profitable (Leonard *et al.*, 1976; Lloyd,

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1977), efforts should be made to screen children from high-risk families (Leonard *et al.*, 1976). Many children from families with accelerated CHD and hypercholesterolaemia will also have raised plasma lipids (Tamir *et al.*, 1972).

However, recent evidence has suggested that measurement of lipids only may be insufficient to assess the true risk for CHD. For example, Glueck *et al.* (1978a) reported that about 16% of schoolchildren with raised plasma TC levels had normal concentrations of LDL and the increase in TC was due solely to raised plasma HDL. In view of the protective effect of HDL, these children were putatively at a lower risk for CHD, which obviated the need for intervention.

We report on the distribution of serum lipids and lipoproteins in 67 children from 33 high-risk families, and reiterate the need to measure lipoproteins, in addition to TC and triglyceride (TG), for the correct diagnosis of abnormalities in such children.

Patients and methods

67 children (38 boys and 29 girls) aged between 2 and 16 years (mean 8·8) were investigated. They were the offspring of 33 hypercholesterolaemic (that is—serum TC >95th centile) fathers and normolipaemic mothers. Serum TG concentrations in all the fathers were normal. The fathers of 31 children had a history of CHD verified from hospital records (pathognomonic ECG changes and increased serum enzymes), whereas in the fathers of 36 children there was no history of atherosclerosis. All the fathers were less than 44 years old at the time of examination.

For comparative purposes, we also measured serum lipids and lipoproteins in 19 children (mean age 11·6; range 2–17 years) whose parents were normolipaemic and had no history of atherosclerosis.

Blood samples were obtained after an overnight fast (at least 12 hours). Children under 5 years were allowed water until 2 hours before examination. Serum TC was estimated by the method of Rappaport and Eichhorn (1960) and TG by the method of Shafrir and Khassis (1969). Because TG concentrations were <3·25 mmol/ (<298 mg/100 ml) in all samples, HDL-cholesterol (HDLc) was assessed by precipitation of the very low density lipoprotein (VLDL) and LDL with a heparin-manganese chloride solution and measurement of the cholesterol content of the supernatant. VLDL-cholesterol was assumed to be equal to serum TG/2, and LDL-cholesterol (LDLc) was calculated as the quantity: TC-HDLc-VLDLc.

Results

The concentrations of serum lipids and lipoproteins in the three groups of children are shown in Tables 1 and 2. For all the parameters studied, no statistically significant differences were found between the children of fathers without CHD (group 1) and the children of fathers with CHD (group 2). Therefore, these two groups were combined for subsequent analyses. The children from the high-risk families (groups 1 and 2) had significantly higher levels of TC ($P<0\cdot01$), and LDLc ($P<0\cdot001$), than the children in the control group. No significant differences were detected in the concentration of TG or HDLc.

The Figure shows that in 30 (40%) of the high-risk children, TC concentrations exceeded the mean level of the control group by >2 SDs. In three of these, serum TG levels were also raised. One child had normal TC but an increased TG level. Of the 30 children in whom hypercholesterolaemia was present, only 23 had high TC levels resulting from raised LDLc. In 7 children, the TC levels were high but LDLc concentrations were normal. In these 7 children HDLc exceeded the mean of the control

Table 1 *Mean (± SD) serum lipid and lipoprotein levels in children with hypercholesterolaemic and normolipaemic parents*

Group	*Age (years) (mean, range)*	*TC (mmol/l)*	*TG (mmol/l)*	*LDLc (mmol/l)*	*HDLc (mmol/l)*
1 (n = 36)	8·3 (2–16)	5·58±1·62	0·61±0·29	3·67±1·38	1·68±0·38
2 (n = 31)	9·5 (3–16)	5·34±1·00	0·57±0·30	3·41±0·90	1·64±0·40
P		NS	NS	NS	NS
1 and 2 (n = 67)	8·9 (2–16)	5·47±1·36	0·58±0·29	3·55±1·16	1·66±0·38
Control (n = 19)	11·6 (2–17)	4·46±0·64	0·69±0·29	2·56±0·64	1·57±0·38
P		<0·02	NS	<0·001	NS

Group 1 were children with normolipaemic mothers and hypercholesterolaemic fathers who had a history of MI. Group 2 were children with normolipaemic mothers and hypercholesterolaemic fathers who had no history of MI.
TC = Total cholesterol, TG = triglyceride, LDLc = low-density lipoprotein cholesterol, HDLc = high-density lipoprotein cholesterol.
Conversion: SI to traditional units—cholesterol: 1 mmol ≈ 38·6 mg/100 ml, triglyceride: 1 mmol ≈ 88 mg/100 ml.

Table 2 *Total cholesterol and lipoprotein cholesterol (means) in children from 'high-risk' families with raised* TC but normal LDLc levels*

Case	*Age (years)*	*Sex*	*TC (mmol/l)*	*LDLc (mmol/l)*	*HDLc (mmol/l)*	*VLDLc (mmol/l)*
1	13	F	5·77	2·86	2·26	0·65
2	8	M	5·87	3·67	2·00	0·23
3	11	F	6·16	3·27	2·65	0·23
4	14	M	5·95	3·27	2·31	0·36
5	8	F	5·79	3·35	2·26	0·18
6	7	M	5·85	3·22	2·31	0·31
7	11	M	6·34	3·64	2·31	0·39

*Exceeding the mean for control group by > 2 SDs.

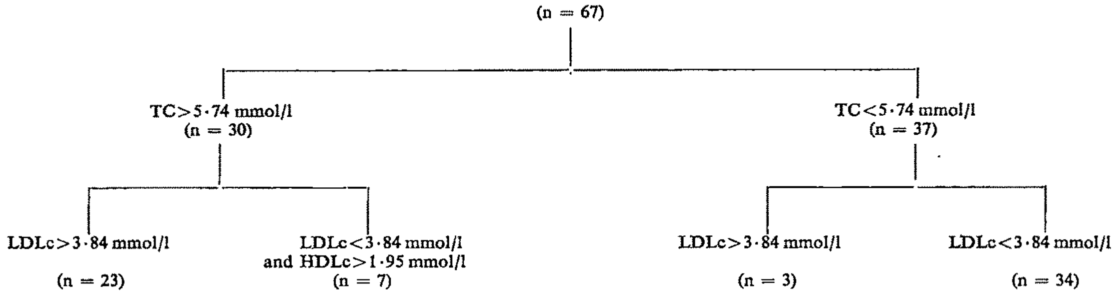

Figure *Total number of children at high risk.*

group by 1 SD, and thus was the main contributor to the raised TC levels. In 3 children, raised levels of LDLc (>3·84 mmol/l) were accompanied by low HDLc (<1·19 mmol/l), resulting in normal TC (<5·74 mmol/l).

Discussion

The importance of detecting risk factors for CHD as early as possible in childhood is now well accepted (Glueck *et al.*, 1974; Levy and Rifkind, 1974; Lauer *et al.*, 1975). It is assumed, but not yet confirmed, that instituting measures to correct these risk factors early in childhood will prevent, or at least delay, the onset of atherosclerosis and its main manifestation—CHD.

Raised plasma or serum lipids, mainly TC, are among the main factors that are especially associated with increased risk for CHD in young adults (Kannel *et al.*, 1971; Blackburn, 1974; Keys, 1975; *Lancet*, 1977). Moreover, the risk for developing early atherosclerosis is particularly high in patients with FH, especially in young men (Slack, 1969; Stone *et al.*, 1974). Hence, screening children to detect FH is recommended by some but not all paediatricians (Lloyd, 1975). However, it is generally agreed that children from high-risk families—that is families with a history of accelerated atherosclerosis or hyperlipoproteinaemia—should be examined for detection of FH (Tamir *et al.*, 1972; Glueck *et al.*, 1974; Leonard *et al.*, 1976; Lloyd, 1977).

Diagnosis of FH is usually based on a raised level of TC or LDLc in the propositus and in at least one first-degree relative. However, because about 70% of plasma TC is carried in the LDL, it has been generally accepted that in most instances measurement of TC is sufficient for appropriate diagnosis.

The importance of the inverse relationship of HDLc and CHD has been reported (Tyroler *et al.*, 1975; Glueck *et al.*, 1976; Castelli *et al.*, 1977) and HDL is now considered a 'negative risk factor' for CHD. Measurement of lipoproteins is thus assuming greater importance for proper diagnosis and treatment. In addition to the study by Glueck *et al.* (1978a), in which up to 16% of a group of schoolchildren with raised TC levels had normal LDLc but increased HDLc, it has also been shown that about one-third of children referred because of hypercholesterolaemia had increased concentrations of HDLc with normal LDLc (Neill *et al.*, 1977). Curiously, these children are putatively at a lower risk for CHD, in spite of their raised TC levels.

In 10 (15%) of the 67 children reported here, the correct diagnosis would have been missed if TC and TG alone had been measured. In 7, the increased TC levels were caused by increased concentrations of HDLc (with normal concentrations of LDLc). These children probably have a lower than normal risk for developing CHD; therefore, any measures aimed at reducing their TC are probably not warranted. At the same time, however, the normal TC levels in 3 children were the result of increased LDLc but low HDLc. These children, who are probably at the highest risk for CHD (Kwiterovich, 1977), would also have been missed had only TC been estimated.

Our results confirm earlier reports that approximately 40% of the children born to matings of familial hypercholesterolaemic and normolipaemic parents will have FH (Tamir *et al.*, 1972; Kwiterovich *et al.*, 1974). The need for accurate diagnosis is especially important in the children from these high-risk families; it is likely that they carry the genetic form of hypercholesterolaemia, which has been shown to be associated with a very high risk for CHD.

We advocate measurement of lipoproteins in these children—although it is more complex and requires special skill and equipment—as it clearly enhances diagnostic precision and improves the assessment of their risk. Furthermore, it facilitates appropriate treatment and prognostication. This is important not only for the fortunate children whose raised TC levels result from raised HDLc, who are thus putatively at lower risk for CHD, but it is of vital importance for the children whose normal TC levels (but low HDLc) do not accurately reflect their high-risk status.

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Folate nutrition and growth in infancy

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SUMMARY The effect of suboptimal folate nutrition on the growing infant was studied in a population of infants fed a diet based on boiled, pasteurised cows' milk. One group of infants received a daily supplement of 1 mg folic acid from age 2 months, while the other group received a placebo. The infants were seen at bimonthly intervals. In the supplemented group the red cell folate level had increased to twice its pretreatment value by 4 months, and remained at this high level to the end of the first year. Hb concentration and incidence of anaemia were similar in both groups. The incidence of infection in the two groups did not differ. Weights and lengths attained at 6 months, and the rate of gain from 2 to 6 months were higher in infants whose folate levels were above the median value than in those below it. In the second half of the first year the differences between the two groups were no longer evident.

The classical description by Zuelzer and Ogden (1946) of folate-responsive megaloblastic anaemia of infancy drew attention to the fact that young babies were a group particularly at risk for folate deficiency. Interest subsequently focused largely on megaloblastic anaemia as a manifestation of folate deficiency. Other, less obvious effects of suboptimal folate nutrition are less well documented.

The present study was initiated to detect any effects of folate undernutrition on the growing infant. The study was facilitated by the practice of infant feeding current in Israel, which is based on the use of boiled pasteurised cows' milk. Milk treated in this manner has been shown to be a poor source of folate. Furthermore, infants fed such a diet tend to have low blood-folate levels (Matoth *et al.*, 1965). It was therefore of interest to investigate whether a population of apparently healthy infants fed the standard diet and presumed to be suboptimally provided with folate was in any way inferior to a folate-replete group, created by the daily administration of large doses of folic acid.

Study population and methods

The study was carried out in Rosh Ha-Ayin in central Israel. This community was chosen because it is uniformly inhabited by Yemenite Jews who immigrated to Israel in 1949–50 and therefore represent a homogeneous population with respect to ethnic and cultural backgrounds as well as to socioeconomic status. The Rosh Ha-Ayin area is served by two child health clinics. Each infant attending clinic A received a daily supplement of 1 mg folic acid in the form of a specially prepared tablet, while those attending clinic B received a placebo. Supplementation was started at 2 months and the infants were seen at regular bimonthly intervals from age 2 months to one year. The red cell folate levels, Hb concentrations, weights and lengths were determined at each visit. At each clinic the infants were weighed and measured by the same experienced trained nurses. The incidence of infection was monitored and recorded.

100 term infants whose birthweights were >2·5 kg were studied. The male:female ratio was 53:47 in clinic A and 49:51 in clinic B. The attendance was practically complete. It was therefore possible to terminate the study when the first 53 infants in clinic A and the first 60 in clinic B had reached age one year. The mothers did not know which infant was receiving the active material. Each was informed of the potentially beneficial effects of folic acid, and her consent to enrolling the infant in the trial and her co-operation were obtained.

Folate in whole blood was determined with a micromethod using 0·1 ml skin prick blood. The procedure of Cooperman (1967) was followed. The

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method has been in routine use in our laboratory for the last 10 years and has given consistent results. The folate values obtained with this method are higher than those recorded in our earlier publications (Matoth *et al.*, 1965). Red cell folate was calculated by multiplying the values found in whole blood by 100 ÷ haematocrit.

Results

Red cell folate values, determined at bimonthly intervals from 2 months to one year of age in the infants supplemented with folate (clinic A) and in the unsupplemented group (clinic B), are shown in Table 1. The initial values, obtained at 2 months before supplementation was begun, were similar in both groups. Thereafter, folate values in babies from clinic B remained low at 4 and 6 months and showed a moderate increase subsequently. In contrast, supplementation with folic acid (clinic A) more than doubled the red cell folate at 4 months, and this high level was maintained throughout the first year.

It can be seen from Table 1 that the increase in folate had no effect on Hb concentration, which remained very similar in the two groups throughout the period of observation. The mean values in both groups tended to decrease in the second half of the first year. This was due to the occurrence of anaemia. 15 infants in clinic A and 11 in clinic B had Hb <10 g/dl when they were between 8 and 12 months; the anaemia was caused by iron deficiency. They were given treatment with iron and excluded from further study.

Of 357 episodes of acute gastroenteritis and respiratory infection recorded during the period of observation, 164 were in babies from clinic A and 193 from those at clinic B. The difference was, however, not significant.

In the group of infants supplemented with folic acid from age 2 months, the weights and lengths attained at 4 and 6 months were significantly higher than in the unsupplemented group. The difference was no longer evident in the second half of the first year (Table 1). The relation of changes in weight and length to the folate status was further evaluated by combining the babies from both clinics and comparing, for each age group, infants whose folate levels were above the median value with those whose

Table 1 *Red cell folate levels, haemoglobin concentrations, weights, and lengths in infants supplemented (clinic A) and unsupplemented (clinic B) with folic acid, mean ± SE*

Clinic	*Months*					
	2	*4*	*6*	*8*	*10*	*12*
Red cell folate (μg/l)						
A	254 ± 8·5	502 ± 27·5	539 ± 35·6	595 ± 43·0	550 ± 54·1	514 ± 33·2
B	237 ± 9·5	219 ± 9·7	217 ± 00·1	282 ± 20·4	274 ± 17·6	292 ± 24·5
Haemoglobin concentration (g/dl)						
A	10·79 ± 0·11	11·13 ± 0·11	11·00 ± 0·11	10·83 ± 0·15	10·34 ± 0·18	10·27 ± 0·17
B	11·35 ± 0·15	11·30 ± 0·10	11·29 ± 0·10	10·93 ± 0·13	10·60 ± 0·13	10·38 ± 0·14
Length (cm)						
A	53·61 ± 1·01	62·40 ± 0·28*	67·30 ± 0·32*	69·38 ± 0·97	70·07 ± 1·83	74·79 ± 0·38
B	54·59 ± 0·22	61·58 ± 0·28	66·14 ± 0·26	68·76 ± 0·28	90·96 ± 0·27	73·68 ± 0·35
Weight (kg)						
A	4·70 ± 0·07	6·53 ± 0·07*	7·71 ± 0·08*	8·47 ± 0·15	9·03 ± 0·25	9·72 ± 0·14
B	4·51 ± 0·05	6·12 ± 0·07	7·35 ± 0·09	8·10 ± 0·10	8·88 ± 0·12	9·44 ± 0·12

*Significantly higher than corresponding value in clinic B (P <0·05).

Table 2 *Weights and lengths of infants with high and low folate levels, mean ± SE*

Folate level	*Months* *2*	*4*	*6*	*8*	*10*	*12*
Red cell folate (μg/l)						
High	310 ± 8	527 ± 25	557 ± 31	658 ± 37	551 ± 38	526 ± 25
Low	183 ± 4	186 ± 5	179 ± 6	200 ± 8	191 ± 9	208 ± 9
Weight (kg)						
High	4·699 ± 0·61	6·549 ± 0·07*	7·789 ± 0·09*	8·489 ± 0·15*	9·052 ± 0·19	9·803 ± 0·13
Low	4·518 ± 0·65	6·096 ± 0·0	7·240 ± 0·08	8·069 ± 0·10	8·817 ± 0·13	9·377 ± 0·13
Length (cm)						
High	53·31 ± 0·98	62·39 ± 0·27	67·29 ± 0·31*	69·42 ± 0·97	70·55 ± 1·24	74·74 ± 0·3
Low	54·95 ± 0·24	61·66 ± 0·29	66·02 ± 0·26	68·69 ± 0·29	70·74 ± 0·53	73·78 ± 0·38

High and low folate = folate levels above and below median.
*Significantly higher than corresponding 'low folate' value (P <0·05).

Table 3 *Changes in weights and lengths from 2 to 6 months in infants with high or low folate levels, mean ± SE*

Folate level	*At 6 months*		*Increment from 2 to 6 months*	
	Weight (kg)	*Length (cm)*	*Weight (kg)*	*Length (cm)*
High	7·789 ± 0·09	67·293 ± 0·310	3·134 ± 0·077	13·326 ± 0·866
Low	7·240 ± 0·08	66·02 ± 0·265	2·743 ± 0·070	11·472 ± 0·244
P	<0·001	0·002	<0·001	0·042

High and low folate = folate levels above and below the median value at 6 months.

levels were below it (Tables 2 and 3). Weights and lengths at 6 months were significantly higher in the high folate than in the low folate group. In the former, weights were higher also at 4 and 8 months. As shown in Table 3, the rate of gain in weight and length from 2 to 6 months, calculated from individual increments, was significantly higher in the high folate group.

Discussion

It is evident from our data that growth can be enhanced in apparently healthy infants by providing them with an abundant supply of folic acid. Conversely, it may be concluded that a shortage of folate can be a limiting factor to growth. This is not surprising, as it is well known that folates are essential for DNA and RNA synthesis. Accordingly, the folate requirements for cell proliferation in the rapidly growing organism are very high. The fetus is well endowed with folate at birth. Soon after, the blood folate level decreases and reaches a low point at 6 to 8 weeks (Matoth *et al.*, 1964a). From that age on the infant depends entirely on diet for its folate needs. The age group 2 to 6 months is, therefore, a critical period. On the one hand, this is a period characterised by a high growth rate and, accordingly, maximal folate requirements. If, on the other hand, intake is marginal, as is the case in our population, shortage of folate may affect growth. In the second half of the first year, as growth slows down, there is a relative decrease in folate requirements. At the same time intake is increased by the introduction of folate-rich foods. As a result, the infants achieve a better folate balance and catch up in weight and length with their folate-replete fellows.

There are few reports dealing with the effects of folate deficiency on growth. The administration of 50 μg folic acid per day to low birthweight infants did not increase their weight at 6 months (Kendall *et al.*, 1974). More recently, Gandy and Jacobson (1977a) found in infants with erythroblastosis fetalis a tendency to low serum-folate, which persisted throughout the first year of life. In these infants there was a strong correlation between low serum-folate and the rate of weight gain. It is of interest that supplements of 2·5–5 mg folic acid given to erythroblastotic infants resulted in an increase in the rate of weight gain at 4 months, compared with non-supplemented erythroblastotic controls (Gandy and Jacobson, 1977b).

In the present study, folate shortage of a degree sufficient to cause a measurable deceleration of growth did not affect Hb concentration. The incidence of anaemia was similar in the folate-rich and folate-poor groups. Anaemia, when present, bore the mark of iron deficiency. Furthermore, it occurred late in the first year, at a time when folate shortage, as shown by its effect on growth, was no longer evident. The high incidence (26 cases) of anaemia in our material reflects the prevalence of iron deficiency in babies in Israel.

In a previous study (Matoth *et al.*, 1964b), hospitalised infants with a wide range of Hb and folate levels showed no correlation between these two variables. It appears therefore that, even in a population of infants with relative shortage of folate, iron deficiency is the dominant factor in nutritional anaemia, whereas folate deficiency of a degree of severity or duration necessary to produce anaemia is uncommon.

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The following articles will appear in future issues of this journal:

Human growth hormone (UK). *R. D. G. Milner.*

A prospective study of 18 infants of chronic HBsAg mothers. *F. Mollica, S. Musumeci, S. Rugolo, and T. Mattina.*

Virus infections in children with acute lymphoblastic leukaemia. *A. W. Craft, M. M. Reid, P. S. Gardner, E. Jackson, J. Kernahan, J. McQuillin, T. C. Noble, and W. Walker.*

Oral fat loading test: a reliable procedure for the study of fat malabsorption in children. *A. Jonas, S. Weiser, P. Segal, and D. Katznelson.*

Confirmation of gestational age by external physical characteristics (total maturity score). *J. I. Cater.*

Takayasu's arteritis as a differential diagnosis of systemic juvenile chronic arthritis. *E. Rossor.*

Archives of Disease in Childhood, 1979, **54,** 703–706

Nutritional status of light-for-date infants at birth and its influence on early postnatal growth

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SUMMARY The ponderal index (PI) (g/cm^3 × 100) was used to define the state of nutrition at birth of 47 light-for-date (LFD) term infants and to determine how intrauterine undernutrition influences growth during the first 6 months of postnatal life, at four age intervals: birth–4, 5–8, 9–12, 13–26 weeks. With the exception of one baby, each PI was <50th centile on the Miller and Hassanein standards: in 24 (51 %) babies the PI was <3rd centile. This suggests that, generally, LFD infants are underweight for length, and by inference, are likely to have experienced intrauterine undernutrition. In the first month the 24 'wasted' infants (PI <3rd centile) gained more rapidly in weight, and grew more quickly in head circumference and length than the 16 'nonwasted' infants (PI >10th centile). Thereafter growth rates were similar. With the exception of weight in the 'nonwasted' infants during the first month, rates of growth (weight, length, and head circumference) in both groups of babies in each of the 3 months after birth were greater than in normal infants. The first 3 months after birth can therefore be defined as the period of 'catch-up' growth in LFD term infants.

From their outward appearance light-for-date (LFD) infants who show no signs of congenital malformations or intrauterine infection can be differentiated according to the extent to which they show external signs of intrauterine undernutrition. Some show unmistakable features of wasting while others seem to show none, resembling instead 'perfect miniatures'. Little is known about postnatal growth after intrauterine undernutrition as no study of growth in LFD infants (for example Babson, 1970; Fitzhardinge and Steven, 1972; Brandt, 1976; Martell *et al.*, 1978) has paid regard to the state of nutrition at birth. In the present study we used the ponderal index (PI) (Miller and Hassanein, 1971; Jarai *et al.*, 1977) to investigate the nutritional status of LFD infants at birth, and to see how intrauterine undernutrition affects growth during the first 6 months of postnatal life.

Materials and methods

Study infants. 47 consecutively born term infants were studied: all were white and singletons. None had any congenital malformation or any external feature of intrauterine infection. The weight of each infant was <5th centile for gestation, allowing for sex, mother's height, and birth order (Tanner and Thomson, 1970). Weight, length, and head circumference were measured (D.P.D.) between 24 and 48 hours of age, using methods previously described (Davies, 1976). For each infant the PI (g/cm^3 × 100) was calculated and according to the distribution on the centile standards of Miller and Hassanein (1971) two groups of infants were defined:

Group 1, 'wasted'
24 infants whose PIs were <3rd centile for gestation.

Group 2, 'nonwasted'
16 infants whose PIs were >10th centile for gestation.

Seven infants in whom the PI was between the 3rd and 10th centiles were not included in the final analysis.

Evaluation of growth. Measurements of weight, length, and head circumference were made (D.P.D.) at 1, 2, 3, and 6 months (±3 days of the projected date). Individual growth velocities were calculated for 4 age intervals (birth–4, 5–8, 9–12, 13–26 weeks). Mean values were calculated and the statistical significance of any differences was tested by Student's *t* test.

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As well as comparing growth rates between the two groups of LFD infants, comparisons were made with infants in whom the rate of intrauterine growth had been normal. For this purpose, velocity growth curves for weight, length, and head circumference were constructed from data on 50 term infants of appropriate weights for gestation, who had also been seen at birth, and at 1, 2, 3, and 6 months (P. W. Wilkinson, unpublished observations).

Results

Distribution of PI. Fig. 1 shows the distribution of each PI for the 47 babies according to the Miller and Hassanein standards. All, except one baby, were <50th centile and 24 (51 %) were <3rd centile.

Birth data. Mean values for gestational age, weight, length, head circumference, and PI at birth in both groups of infants are shown in Table 1. Group 1 infants were on average 83 g lighter and 1 cm longer than those in group 2, but the mean values for head circumference were the same.

Growth. Rates of weight gain, length, and head circumference are given in Table 2. Weight, length, and head circumference growth rates were significantly higher ($P<0 \cdot 01$) in group 1 infants during the first month. Thereafter the growth velocities showed no significant differences.

Figs 2–4 show the velocity growth curves for groups 1 and 2 compared with normal infants. Except for weight in the first month in infants in group 2, the mean curves of weight gain, length,

Table 1 *Birth data in 'wasted' (group 1) and 'nonwasted' (group 2) LFD infants. Mean values (SE of mean)*

Birth data	*Group 1* (*n = 24*)	*Group 2* (*n = 16*)
Gestational age (weeks)	38·3 (0·41)	38·7 (0·36)
Ponderal index: (g × 100/cm³)	2·19 (0·02)	2·43 (0·06)
Weight (g)	2097 (54)	2180 (45)
Crown-heel length (cm)	45·7 (0·79)	44·7 (0·28)
Head circumference (cm)	32·1 (0·24)	32·1 (0·45)

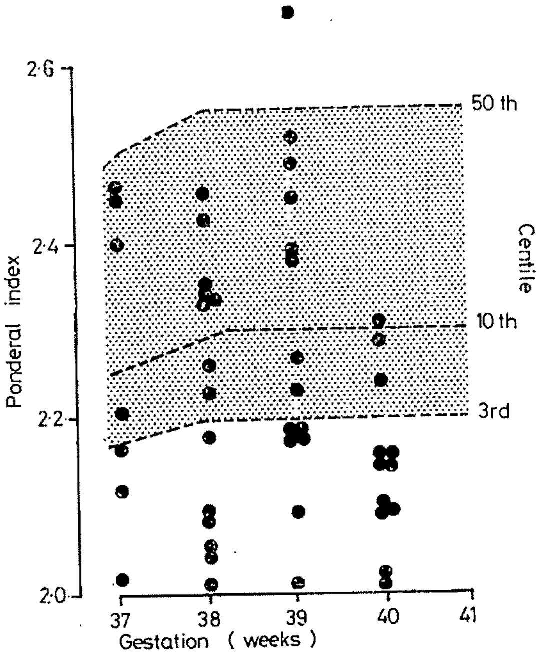

Fig. 1 *Distribution of the 47 ponderal indices on the centile standards of Miller and Hassanein (1971).*

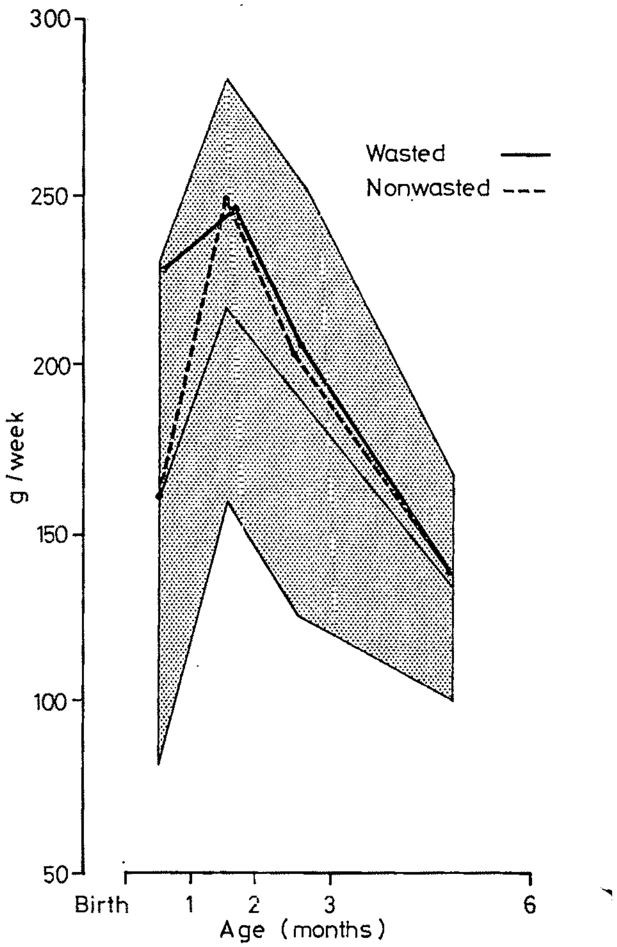

Fig. 2 *Curves of mean weight gain velocities in LFD term infants. Shaded area represents the mean ±1 SD weight gain velocity of 50 normal term infants.*

Table 2 *Comparisons of weekly growth rates in 'wasted' (group 1) and 'nonwasted' (group 2) LFD infants. Mean values (SE of mean)*

Age (weeks)	*Group*	*Weight (g)*	*Length (mm)*	*Head circumference (mm)*
Birth–4	1 (n = 24)	228 (16)	10·5 (0·63)	7·1 (0·34)
	2 (n = 16)	160 (12)	8·6 (0·57)	5·7 (0·56)
	P<0·01			
5–8	1	246 (19)	9·1 (0·48)	5·7 (0·43)
	2	248 (19)	9·8 (0·62)	5·7 (0·39)
9–12	1	207 (13)	7·9 (0·53)	4·1 (0·28)
	2	204 (12)	7·5 (0·54)	4·0 (0·35)
13–26	1	142 (14)	5·1 (0·51)	2·4 (0·31)
	2	143 (14)	4·8 (0·34)	2·7 (0·29)

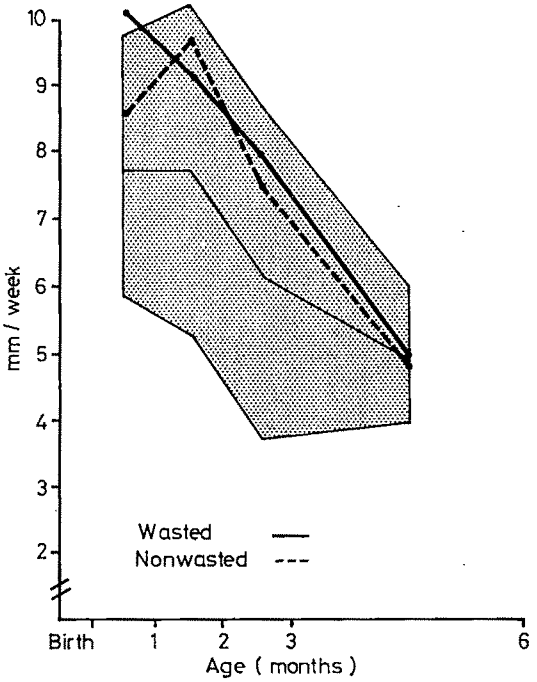

Fig. 3 *Curves of mean length growth velocities in LFD term infants. Shaded area represents the mean ±1 SD length growth velocity of 50 normal term infants.*

and head circumference growth in infants in both groups were consistently higher than those for normal infants during the first 3 months. At between 3 and 6 months the growth rates in both LFD categories were close to normal.

Discussion

The fact that all but one infant had a PI<50th centile at birth suggests that in general LFD infants are underweight for length and likely therefore to have experienced, to a variable extent, inadequate intrauterine nutrition. This is further supported by the observation that 'nonwasted' as well as 'wasted' infants showed above average growth rates in the first 3 months after birth. Campbell showed by intrauterine biparietal cephalometry that as many as 20 to 30% of LFD infants at birth had symmetrical growth retardation due to reduced fetal growth potential (Campbell, 1974). Our data suggest that the proportion of LFD infants who show symmetrical growth retardation is smaller. Indeed our two groups might have been more appropriately termed 'wasted' and 'not-so-wasted' as there would appear to be a continuum of intrauterine undernutrition from those severely affected to those much less affected.

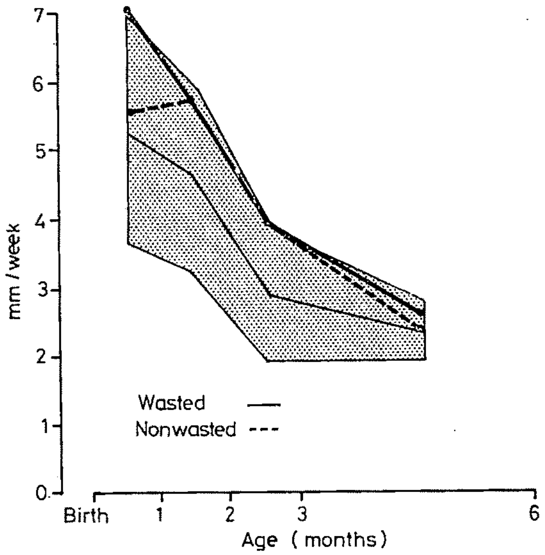

Fig. 4 *Curves of mean head circumference growth velocities in LFD term infants. Shaded area represents the mean ±1 SD head circumference growth velocity of 50 normal term infants.*

In view of the greater than normal growth rates in LFD infants in the first 3 months, this period can be defined as 'the catch-up period'. Furthermore, the fact that during the first month the infants in group 1 grew more rapidly than those in group 2 suggests that much of the intrauterine growth deficit is made up very early in postnatal life. These observations are at variance with Widdowson (1974) who, in a study of the effects of intrauterine undernutrition on postnatal growth in small animals wrote: 'In animals, the rate of growth after birth is related to the size at birth, and the same on the whole is true in man.' Our data show that this is clearly not the case for the newborn human infant who has been underfed in intrauterine life.

We thank the mothers of all the babies who participated in this study, several of our colleagues for criticism, and Mrs F. Quinton and Miss S. Mangal for secretarial assistance.

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Non-neuropathic Gaucher disease presenting in infancy

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SUMMARY The non-neuropathic form of Gaucher disease was diagnosed in 11 children of non-Jewish ancestry in South Africa; all were under the age of 4. None had any neurological involvement and, apart from the precocious presentation and rapid course, the features in each resembled those of the classical 'adult' or chronic non-neuropathic form of Gaucher disease. By contrast, the condition presented after puberty in 24 out of 28 Ashkenazi Jews who were studied during the same investigation. Activity of β-glucosidase was defective in both groups of patients and they could not be distinguished by histological criteria. Only one child with the infantile neuropathic form of Gaucher disease was identified during the survey. The preponderance of the atypical non-neuropathic form of the disorder in young children is of practical importance from the point of view of differential diagnosis in any child with hepatosplenomegaly.

Gaucher disease is conventionally classified into three types: the adult or chronic non-neuropathic, the acute neuropathic infantile, and the subacute neuropathic juvenile (Fredrickson and Sloan, 1972).

The adult or chronic non-neuropathic form is characterised by splenomegaly, dyshaemopoeisis, and orthopaedic complications, in the absence of any neurological involvement. This entity has an overwhelming predilection for Ashkenazi Jews and is by far the most common form of Gaucher disease (Matoth and Fried, 1965). In the infantile type cerebrosides accumulate in the brain and death occurs before age 2. The rare, poorly defined juvenile type has onset in later childhood, involvement of the central nervous system, and a subacute course.

In a survey of all forms of Gaucher disease in South Africa in which 46 patients were investigated we found 13 young children with non-neuropathic Gaucher disease. In 11 of these, the disorder was diagnosed by age 4. As this condition usually presents in adulthood, this precocious onset is a matter of considerable clinical importance. A typical case is reported and details of the manifestations in the other affected children are tabulated and discussed in order to arouse diagnostic awareness and to emphasise that the non-neuropathic form of Gaucher disease can occur in infancy.

Patients and methods

Since 1971, attempts have been made to examine and investigate every patient with Gaucher disease in South Africa. So far 46 with the chronic non-neuropathic form have been studied and in each the diagnosis was confirmed histologically or by demonstration of defective leucocyte β-glucosidase activity. Of these patients 28 were Ashkenazi Jews, 10 were Afrikaners, 3 were of mixed ancestry, 2 were African Negroes, and 3 were British. The survey methodology and the findings in the Ashkenazim have been reported elsewhere (Beighton and Sacks, 1974; Myers *et al.*, 1975; Goldblatt *et al.*, 1978). The genetic implications of Gaucher disease in the Afrikaners, including 7 of the patients in the present series, have also been reported (Goldblatt and Beighton, 1979b).

Surprisingly, the so-called 'adult' non-neuropathic form of Gaucher disease was diagnosed before age 4 in 11 patients, and at 6 and 8 years in 2 others. Apart from a pair of siblings in a Sephardic-Ashkenazi family, all these children were Afrikaners or of mixed ancestry. By contrast, the condition was clinically apparent in only 4 of the 28 Ashkenazi Jews before puberty and their symptoms were slight.

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The classical infantile neuropathic form of Gaucher disease was found in only one patient, a baby born to a consanguineous Indian couple.

Personal and clinical data on the children with non-neuropathic Gaucher disease are shown in the Table, and a brief case report is given below.

Case report. Case 9, the only child of nonconsanguineous parents of mixed ancestry was born in 1974. He weighed 2·6 kg at birth and his neonatal course was complicated by jaundice, for which he received phototherapy.

He had several episodes of croup and bronchospasm during infancy and, at age 2, hepatosplenomegaly was detected during routine examination. Histological studies of bone marrow were undertaken and the diagnosis of Gaucher disease was established. Up to this point, his developmental milestones had been normal.

He was then lost to follow-up until, at age 3½, he again presented with shortness of breath and pyrexia. At this stage his abdomen was distended by a huge spleen which extended into the right iliac fossa, and the liver projected 10 cm below the inferior costal border (Figure). No abnormality could be detected in his central nervous system.

At this time he was pancytopenic with Hb 6·3 g/dl, a platelet count of $35 \cdot 0 \times 10^9$/l and total WBC of $3 \cdot 4 \times 10^9$/l, of which 8% were polymorphs.

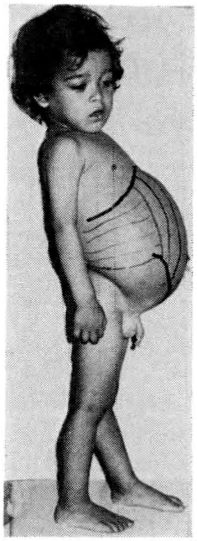

Figure *3-year-old child (Case 9) with Gaucher disease. Massive hepatosplenomegaly is evident.*

During his stay in hospital he had several episodes of massive epistaxis which were attributed to his

Table *Clinical manifestations of children with non-neuropathic Gaucher disease*

Case	*Sex*	*Ethnic group*	*Age at diagnosis (years)*	*Presenting feature*	*Complications*			*Management*	*Family history*
					Skeletal	*Haematological*	*Other*		
1	F	Afrikaner	1½	Splenomegaly	—	Hypersplenism	—	Splenectomy	—
2	F	Afrikaner	3½	Splenomegaly	Pseudo-osteomyelitis	Thrombocytopenia	—	Splenectomy	Brother (Case 3)
3	M	Afrikaner	3½	Splenomegaly. Epistaxis	Bone pain	Thrombocytopenia	—	Splenectomy	Sister (Case 2)
4	F	Afrikaner	2	Splenomegaly	Pseudo-osteomyelitis. Pathological fractures	Hypersplenism	Pulmonary infiltration. Sexual infantilism. Died age 16	—	—
5	M	Afrikaner	6	Hepatosplenomegaly	—	Hypersplenism	Recurrent respiratory infections	—	Affected sister?
6	F	Afrikaner	1	Hepatosplenomegaly	—	—	—	—	2 adult relatives affected
7	F	Mixed ancestry	8	Hepatosplenomegaly	—	Thrombocytopenia	—	—	Brother (Case 8)
8	M	Mixed ancestry	3½	Respiratory infections. Anaemia	—	Thrombocytopenia	Recurrent respiratory infections	—	Sister (Case 7) 3rd sibling probably affected
9	M	Mixed ancestry	2	Hepatosplenomegaly	Rib and clavicle involvement	Hypersplenism	Recurrent respiratory infections	—	—
10	M	Afrikaner-Hungarian	1½	Hepatomegaly	Arthritis. Fractured femoral neck	—	—	Splenectomy	—
11	F	Ashkenazi-Sephardic	4	Malaise. Splenomegaly	—	Hypersplenism	—	—	Sister (Case 12)
12	F	Ashkenazi-Sephardic	3	Croup. Splenomegaly	—	Hypersplenism	—	—	Sister (Case 11)

thrombocytopenia. Cardiac failure developed after numerous blood transfusions, and treatment with digitalis was eventually needed.

β-Glucosidase activity in cultured fibroblasts obtained after skin biopsy was markedly diminished. His mother had intermediate levels of activity in her own cultured fibroblasts, and this was taken to be indicative of her status as a heterozygote for the Gaucher disease gene. The father was not available for investigation.

The patient is now aged 3¾ years. He experiences considerable malaise and his activity is impaired by the gross distension of his abdomen. He has severe hypersplenism and chronic anaemia with a large heart and borderline cardiac failure. His prognosis is considered to be poor.

Discussion

Although they share a common autosomal recessively inherited defect of the enzyme β-glucosidase (Brady, 1978), it is generally accepted that the infantile, juvenile, and adult or non-neuropathic forms of Gaucher disease are separate conditions. At a clinical level death from central nervous system involvement in the infantile and juvenile types, and the prolonged course and absence of neurological complications in the adult form, represent obvious distinctions between these entities.

The ethnic predilection of the adult form of Gaucher disease for the Ashkenazim is well known and in the Jewish community of South Africa this condition is present in about one in 4000 (Goldblatt and Beighton, 1979a). None of our Ashkenazi Jewish patients with this type of the disorder had any neurological involvement and only 4 experienced symptoms before puberty, and these were slight. By contrast, with the exception of the pair of siblings with an Ashkenazi father and a Sephardic mother, none of the 11 children who developed symptoms before age 4 was Jewish. In these children there were no changes in the central nervous system and, apart from the precocious onset and rapid progression, the disease followed the same general course as in the Jewish patients.

The reason for this temporal discrepancy in the development of the disorder is unknown although at a fundamental genetic level allelism or epistasis could be invoked as possible explanations. In view of the nature of our survey methodology, it is unlikely that ascertainment bias or inadequate case investigation could be responsible for this paradox. It is interesting that there was no correlation between the magnitude of the enzymatic defect and the severity of clinical manifestations in any patient.

The occurrence of non-neuropathic Gaucher disease in infancy was noted 40 years ago (Aballi and Kato, 1938), but this form of the condition has been ignored in conventional classifications. However, in a report of these infants with hepatosplenomegaly, Schneider *et al.* (1977) drew attention to early onset and rapid progression in certain non-neuropathic cases.

The magnitude of the problem of early presentation is highlighted by the fact that we found only one patient with the classical infantile neuropathic type of Gaucher disease, in contrast with the 13 children who had the atypical non-neuropathic form. This 13-fold preponderance is of considerable importance from the point of view of differential diagnosis in any child with unexplained hepatosplenomegaly.

We thank our colleagues at the Red Cross War Memorial Hospital and other centres for access to their patients, R. A. De Méneaud for the illustration, and Mrs Greta Beighton and Mrs Barbara Breytenbach for typing the manuscript.

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Chorioamnionitis and funisitis due to *Corynebacterium kutscheri*

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SUMMARY When isolated from the female genital tract, diphtheroids are usually regarded as commensal organisms. *Corynebacterium kutscheri* however is a pathogen in laboratory rodents. We report a case in which *C. kutscheri* was isolated as a pure culture from the umbilical cord and from other surface sites in an infant. Histological examination of the cord and membranes demonstrated the organisms within these fetal tissues. The organisms evoked a fetal cellular response. The importance of recognising commensals as potential pathogens in states of altered host resistance is stressed.

Chorioamnionitis (inflammation of fetal membranes and the fetal surface of the placenta) and funisitis (inflammation of the umbilical cord) are often caused by ascending infections from the lower genital tract, and organisms that are regarded as normal commensals in this area are generally responsible. Although diphtheroids are part of the normal flora of the genital tract (Leppäluoto, 1974; Galask *et al.*, 1976) and have been isolated from the placental fetal surface and the fetal membranes (Benirschke and Driscoll, 1967), their pathogenicity is uncertain. As Benirschke and Driscoll (1967) stated, 'Results of cultures *per se*, were inconclusive. Doubtless this was because most of the placentas had traversed the lower genital tract prior to examination, and because the cultures were then taken from the exposed amniotic surface. However, taken in conjunction with other data, bacteriological cultures become very useful'.

It is worth re-emphasising that an 'infection' is usually defined as the invasion and multiplication of an organism within living tissues of the host (Walter and Israel, 1974). This report describes what we believe may be the first case of infection of the fetal membranes and cord in an infant due to a *Corynebacterium* species.

Case report

A baby girl was born prematurely at 26 weeks' gestation to a 42-year-old grand multiparous woman. Labour had started 24 hours earlier and was associated with leakage of amniotic fluid. Further rupture of membranes with discharge of amniotic fluid occurred immediately before birth. The baby was delivered vaginally as a vertex presentation. Apart from the sustained onset of premature labour, the pregnancy had been uneventful.

The infant weighed 980 g with an Apgar score of 3 after one minute and required assisted ventilation. The infant had periodic apnoea during the first 24 hours after delivery and was hypothermic.

Laboratory investigations were undertaken to exclude the possibility of sepsis and the infant was noted to have a WBC of $17 \cdot 4 \times 10^9/l$ with a pronounced 'shift-to-the-left', and 20% of the white cells were 'band cells'. The cord haemoglobin was 16·6 g/dl. No growth was obtained from a blood culture or cerebrospinal fluid specimens. Cultures from the umbilical cord, fetal membranes, rectum, nose, throat, eye, and external ear gave a pure growth of an aerobic Gram-positive bacillus.

Bacteriological studies. The rods were slender and clubbed and some had pointed ends. Staining was irregular and metachromatic granules were present. When cultured on blood agar plates the organisms were greyish in colour with an irregular edge, and measured about 2 mm after overnight incubation. There was no evidence of haemolysis. The organisms fermented sucrose, and produced urease. Nitrate was not reduced and gelatinase was not produced. The organism was identified as *C. kutscheri*, and this was confirmed by the external reference centres at the Hospital for Sick children, Toronto, and the Central Public Health Laboratory, Toronto.

Chest *x*-rays showed bilateral infiltrates which

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increased during the next 24 hours, and these changes were considered to be consistent with a pneumonitis. After treatment with ampicillin and gentamicin there was considerable improvement in the infant's body temperature and a slow resolution of the pulmonary infiltrates was seen on subsequent x-rays. The abnormalities in the blood film disappeared gradually over a week. No organism was recovered at any time from the tracheal aspirates, however, and there was no firm microbiological confirmation of a *C. kutscheri* pneumonitis.

Pathological studies. The placenta, membranes, and cord were available for pathological examination. The placenta weighed 300 g with obvious discoloration of the fetal membranes by multiple, minute, greyish-brown plaques on the amnion. Similar minute plaques, 0·2–0·5 mm in diameter, were identified on the surface of the umbilical cord (Fig. 1). Microscopical examination showed a florid chorioamnionitis and funisitis (Fig. 2). The plaques consisted of minute central necrotic foci with aggregates of mononuclear cells forming a boundary around invading colonies of Gram-positive bacilli (Fig. 3). In some of the organisms metachromatic granules were present. The organisms penetrated into and proliferated within the subamniotic mesenchyme of the fetal surface of the placenta, and Wharton's jelly in the umbilical cord. Fetal inflammatory cells could be seen migrating through the walls of the umbilical vessels in the cord and on the fetal surface of the placenta towards the invading organisms. There was no evidence of inflammation of chorionic villi. The histological appearances were of a chorioamnionitis and funisitis, in which it was possible to demonstrate invading and proliferating organisms, morphologically compatible with those isolated from the surface of the cord and membranes, evoking a fetal inflammatory cellular reaction.

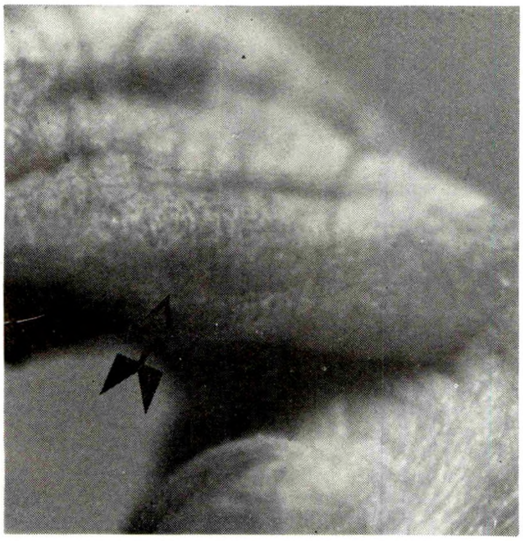

Fig. 1 *Close up view of surface of umbilical cord of infant showing the multiple small greyish-brown plaques (arrow) on its surface (approximately × 2 magnification).*

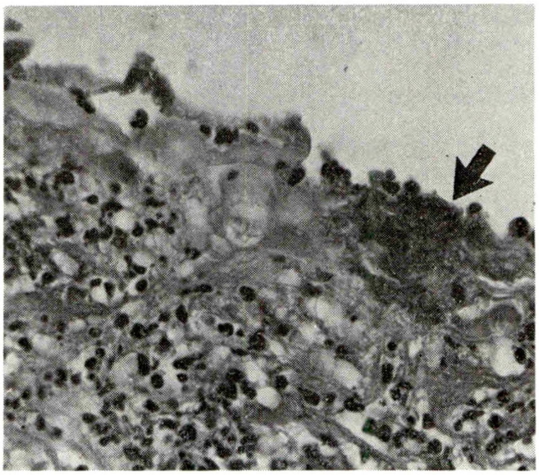

Fig. 2 *Microscopical section through umbilical cord showing the proliferating colony of diphtheroids (arrow) and the cellular inflammatory response in Wharton's jelly. Papanicolaou's stain,* × 800.

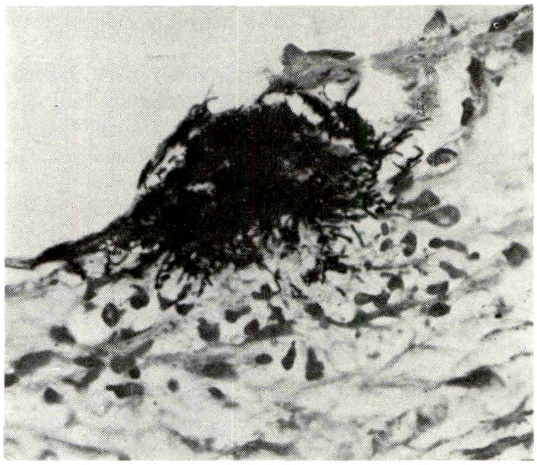

Fig. 3 *Gram stain of one of the plaques seen in Fig. 1, showing the proliferating Gram-positive rods within Wharton's jelly. Note also the early cellular response to the organism. Gram stain,* × 800.

Follow-up. This baby has been followed up repeatedly after being discharged at 11 weeks (postnatal age). Weight gain has been slow, but consistent, and the infant appears otherwise normal in all respects at age 2 years.

Discussion

Ascending infections of the female genital tract are associated most commonly with isolates of *Escherichia coli*, anaerobic cocci, and *Bacteroides* species (Galask *et al.*, 1976), all flora that normally inhabit the female genital tract (Tashjian *et al.*, 1976).

C. kutscheri (formerly classified as *Corynebacterium murium*) has been known to be a cause of pseudotuberculous, granulomatous infection in laboratory rodents (Fauve *et al.*, 1964; Pierce-Chase *et al.*, 1964). However, like other diphtheroids, it is regarded as a normal commensal when isolated from the female genital tract (Galask *et al.*, 1976; Tashjian *et al.*, 1976). Diphtheroids are, of course, recognised often on routine cervical cytological examination in asymptomatic women (Leppäluoto, 1974). In fact, diphtheroids are such common inhabitants of the vagina that they can prove a source of diagnostic confusion as pathogenic *Listeria monocytogenes* may be wrongly classed as diphtheroids (Morison, 1970).

As the fetal skin surface, umbilical cord, placenta, and membranes may be expected to be contaminated with vaginal organisms during their passage through the genital tract (Benirschke and Driscoll, 1967), the isolation of a commensal organism does not on its own constitute proof of its pathogenicity or its aetiological role in producing chorioamnionitis.

As has been shown by many workers (summarised by Benirschke and Driscoll, 1967) diphtheroid organisms are often isolated from a variety of cultures of the vaginal cavity (Weinstein, 1938; Torrey and Reese, 1945), amniotic surface (Driscoll, 1967), and even from cultures of blood sampled through the umbilical cord (Kobak, 1930). In all these reports diphtheroids have never been reported in a *pure* culture, and in no instance was it suggested they were pathogenic.

In our patient however, we have been fortunate in demonstrating the invasion of fetal tissues by an organism that is often regarded as a banal commensal, and have been able to show it inducing an inflammatory response from the fetus. We were successful, furthermore in isolating it as a pure uncontaminated culture. It is possible for us to be confident, therefore, in identifying *C. kutscheri* as the causal agent in our particular infant's chorioamnionitis and funisitis. While we believe that this may be the first case where this organism has been implicated in an infection in humans, it is worth mentioning that the circumstances were fortuitous. It is probable, therefore, that other cases of *C. kutscheri* chorioamnionitis have occurred, but not been recognised or reported.

We believe that in our patient there were sufficient clinical grounds for suspecting a pneumonitis even though we were unable to obtain firm microbiological proof. The improvement in clinical status, in parallel with the changes in the *x*-rays of the chest and amelioration of the haematological abnormalities, after appropriate treatment with antibiotics does not mitigate against this view.

This case indicates the importance of recognising the possible role of commensals as potential pathogens when host resistance may be altered, as in extreme immaturity and in the presence of leaking amniotic fluid, with a breakdown in the natural barriers to infection. In such a situation the isolation of pure cultures, even of commensal micro-organisms, demands careful assessment and close co-operation between microbiologist and pathologist.

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Short reports

Rectal aspirin—absorption and antipyretic effect

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SUMMARY Rectal acetylsalicylic acid was given to 14 children who had undergone open heart surgery. The effect on their temperatures was similar whether 15–30 or 30–50 mg/kg was given. Either dose was more effective than no treatment. The greatest fall in temperature occurred after 4 or 5 hours. Rectal aspirin in a triglyceride base is effective in lowering postoperative temperature. It should also be of use in treating other fevers. A dose of 20–25 mg/kg is suggested.

There are several reasons for raised temperatures in postoperative patients apart from infection. Fluid restriction after some types of surgery, and endogenous pyrogen release by leucocytes are two reasons for such pyrexia. However, there is no evidence that this pyrexia plays any beneficial role in aiding the inflammatory response. On the contrary, the increased metabolic rate resulting from raised body temperature may increase the stress to the patient. It is reasonable therefore to attempt to reduce such pyrexia, particularly after major surgery.

Aspirin is an effective antipyretic, and is better and more comfortable than tepid sponging (Hunter, 1973). There are conflicting reports concerning the usefulness of rectal aspirin (Samelius and Åström, 1958; Nowak *et al.*, 1974), and anyway they concentrated on the urinary recovery of salicylate in healthy subjects, rather than on the clinical effectiveness of rectal aspirin.

This trial was carried out with the following aims: (1) to assess the effect of rectal aspirin in lowering temperature after cardiac surgery; (2) to determine the duration of action of a single rectal dose; (3) to determine a weight-related dose for rectal aspirin; (4) to assess the safety of rectal aspirin.

Patients and method

19 children aged between 3 and 14 years who had undergone open heart surgery were studied. All had arterial and venous cannulae and a pulmonary artery temperature probe in place. Acetylsalicylic acid in a triglyceride base was given as a single dose into the rectum. Suppositories contained either 150 or 300 mg aspirin. Seven of the 19 children were given between 15 and 30 mg/kg, the mean dose being 23 mg/kg. Seven children were given between 30 and 50 mg/kg, with a mean dose of 44 mg/kg. The remaining 5 children were used as controlsy 1 ml blood was obtained before and then hourln for 7 hours after the suppositories had been inserted. Pulmonary artery and peripheral temperature were recorded throughout the trial.

No patient developed a clinically obvious infection for 72 hours after the trial. Serum salicylate was measured using the method of Keller (1947), modified for use in an ABA-100 analyser.

Results

The serum salicylate levels, attained after different doses are shown in Fig. 1. The greatest levels were reached 3 or 4 hours after administration. There was very little fall-off in serum levels up to 7 hours after administration. Levels achieved at any time after the higher dose were almost twice those attained after the lower dose, although the two

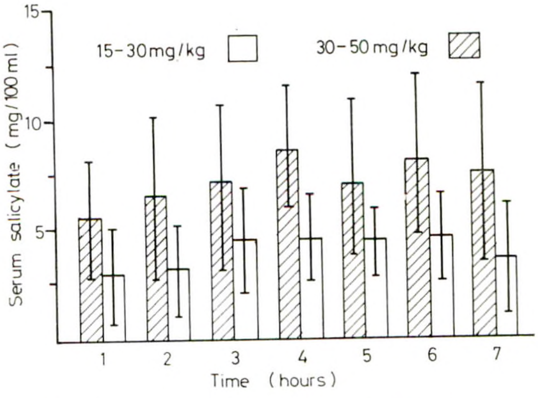

Fig. 1 *Serum salicylate levels (mean ± SD) after rectal acetylsalicylic acid.*

groups overlapped. The highest serum level reached in any patient was 14 mg/100 ml (1·0 mmol/l), 6 hours after insertion of the suppositories. Low serum levels were achieved initially in 2 patients whose core-peripheral temperature gradients were more than 8°C for the first 3 hours of the trial.

The temperature pattern in the three groups is shown in Fig. 2. The mean temperature at the time of administration was somewhat lower in those who received the smaller dose, but throughout the period of observation the temperatures between the three groupings overlapped. The temperatures in those who received no aspirin tended to remain constant. Both groups who received rectal aspirin showed a fall in mean temperature of 0·9–1·0°C. The lowest mean level was reached after 4 hours in the low-dose group and after 5 hours in the high-dose group.

All subjects retained the suppositories throughout the trial, and in no patient did rectal bleeding occur.

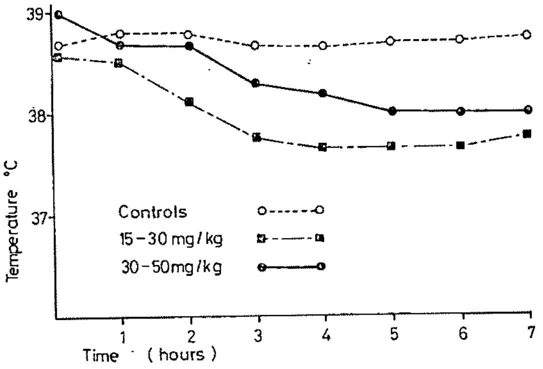

Fig. 2 *Temperature pattern after rectal aspirin.*

Discussion

The peak serum level after oral salicylate is reached after 2 hours (Lowenthal *et al.*, 1970). The peak level after rectal administration occurs later. When a rapid antipyretic effect is sought, the oral route should be used. However, when temperature reduction is not urgent, or in cases where the patient is vomiting or is unable to swallow, the rectal route is a useful alternative. The delay in attaining a peak serum level after rectal administration reduced the incidence of side effects (Borg *et al.*, 1975).

Results reported by Parrott (1971) suggest that the mucosa of the entire gastrointestinal tract has the same absorption characteristics for aspirin. The suppository base used is one factor that may influence absorption from the rectum (Samelius and Åström, 1958; Gibaldi and Grundhofer, 1975). The triglyceride base used in this trial has a melting point of between 33·5 and 35·5°C and a hydroxyl value below 2, and thus it is appropriate to use it for rectal acetylsalicylic administration as long as the rectal temperature is above 33·5°C.

The retention time influences the amount of aspirin absorbed (Nowak *et al.*, 1974). In all subjects in the present study the suppositories were retained throughout the 7 hours, thus a large percentage is likely to have been absorbed.

The overall rate of absorption in the 14 patients was good, although there was individual variation. This was particularly pronounced in the 2 patients with large core-peripheral temperature gradients. It is probable that these 2 had rectal vasoconstriction while the large gradient persisted, resulting in very slow absorption.

The doses used in this trial were higher than those recommended for oral administration. However, the maximum serum level reached in any patient was well below the toxic level. The LD 50 of rectal acetylsalicylic acid in rats is 790 ± 27 mg/kg (Coldwell and Boyd, 1966); the doses used in the present trial were well below this amount.

The optimum serum salicylate level for temperature reduction is not known. The level possibly depends on the aetiology of the pyrexia, and the sex and age of the patient. There is probably individual variation in the response to a given salicylate level.

Our results suggest that 3–5 mg/100 ml is as effective as a level of 5–10 mg/100 ml in postoperative pyrexia. This may be the result of an equal effect on prostglandin levels in the hypothalamus by any serum salicylate level below about 15 mg/100 ml. It is of interest that this level is lower than that needed for an anti-inflammatory or an analgesic effect. Also, the wide range of apparently effective levels is of interest in view of the large variations in plasma levels attained after a given oral dose of salicylate (Bardare *et al.*, 1978). It thus may be reasonable to recommend a dose on a 'per kilogram' basis in spite of the variation in plasma levels after oral rectal salicylate.

We thank Mr D. Kenny and staff in the Biochemistry Department of Our Lady's Hospital for Sick Children for performing the serum salicylate levels, and the nurses in St Patrick's Ward for their help in recording the observations. We also thank Rice Steele & Co. for supplying the suppositories.

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Thrombocytosis in low birthweight infants

A physiological phenomenon in infancy

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SUMMARY Prematurity has traditionally been connected with thrombocytopenia, although this is unlikely to be associated with prematurity itself but rather with serious illnesses in such infants. Platelet counts were measured in 117 healthy preterm infants with birthweights <2000 g, who were followed up from 2 weeks to 6 months. In this series the platelet counts were high compared with those in previous reports, and also compared with what is considered normal for term infants. The 95% range was between 160 and 675 × 10^9/1, with a median value of 375 × 10^9/1. The data suggest that thrombocytosis is a phenomenon related to prematurity.

There have been conflicting reports on platelet counts in preterm infants during the first weeks of life and little information about platelet counts after 2 months. Medoff (1964) found low values in infants with birthweights <1700 g, as did Kaplan and Klein (1962). Aballi *et al.* (1968) reported considerably higher values with a mean value >200 × 10^9/1 at 1–2 days and >300 × 10^9/1 at 2 weeks and at one month in a large series of 300 premature infants. They excluded 10% of the infants because they were ill or subsequently died, and concluded that the abnormally low values in earlier reports might be associated with serious illnesses which result in thrombocytopenia. Evidence of illness was also found in many premature infants who had low platelet values (Oztalay and Beard, 1963). Abnormally high values have been reported in connection with haemolytic anaemia due to vitamin E deficiency (Ritchie *et al.*, 1968). Melhorn and Gross (1971) found platelet counts of between 400 and 450 × 10^9/1 in 10 infants with anaemia, reticulocytosis, and low levels of serum vitamin E concentration who were aged 6–8 weeks. The platelet count subsequently decreased when the infants were treated with oral vitamin E.

The purpose of this study was to establish the platelet counts in preterm infants who were followed longitudinally and for a sufficiently long time to exclude any sick infant; iron and vitamin E deficiency was prevented by giving daily supplements.

Subjects and methods

At age 2 weeks a group of 125 healthy preterm infants with birthweights between 1050 and 2000 g was studied (Lundström *et al.*, 1977). None then had had exchange transfusion, but 7 had transfusions later and so were excluded. One infant with hereditary spherocytosis was also excluded. Thus the study group comprised 117 infants who were tested at 2 weeks and then each month until aged 6 months, on average five times per infant. Gestational age according to amenorrhoea ranged from 27 to 40 weeks (mean 32 weeks); the average birthweight was 1650 g.

During the follow-up period the infants received either breast milk, proprietary infant milk formula, or home-prepared cows' milk dilution. In addition to vitamins A, D, and C, and folic acid, each infant was given a daily dose of 5 IU vitamin E as alpha-tocopherol acetate beginning at age 2 weeks. Thus the ratio of vitamin E to polyunsaturated fatty acids in the three milk diets ranged from 1·6 to 5·0, and exceeded the amount normally considered sufficient to prevent vitamin E deficiency (Horwitt *et al.*, 1963). The infants with uneven birth dates received 2 mg/kg elemental iron each day starting at 2 weeks, while babies born on even dates were not given additional iron before 6 months unless there were signs of iron depletion in their haemoglobin (Lundström *et al.*, 1977).

Hb concentration and reticulocyte and platelet counts were determined from capillary samples during the initial period in hospital and from venous blood at subsequent outpatient visits. Hb was measured by a Model S Coulter Counter. Reticulocytes were determined microscopically. Platelet counts were performed by a direct chamber count method (Wright and Kinnicutt, 1911).

Results

There was evidence of thrombocytosis in preterm infants aged between 2 weeks and 6 months. However, there was a wide range of values at each age and a great variation within single infants at different times (Figure). The 95% range of all the babies with their ages combined was between 160 and 675 × 10^9/l, with a median of 375 × 10^9/l. Only a few infants had transient low values <200 × 10^9/l.

There was no difference in platelet counts between infants who were given iron and those who were not (Figure). At each age the groups of infants with platelet counts above or below 400 × 10^9/l had similar values for Hb and reticulocyte counts, except at 2 weeks of age when the group with the high count had a lower concentration of Hb ($P<0\cdot05$). In order to test the correlation between gestational age and platelet count the two extreme groups, those with gestational age <31 weeks and those with gestational age >34 weeks were compared. No difference was found, nor was there any correlation between birthweight and platelet count.

Discussion

In this series of premature infants the platelet counts were high compared with other reports (Kaplan and Klein, 1962; Medoff, 1964), and also compared with what is considered normal for term infants. In

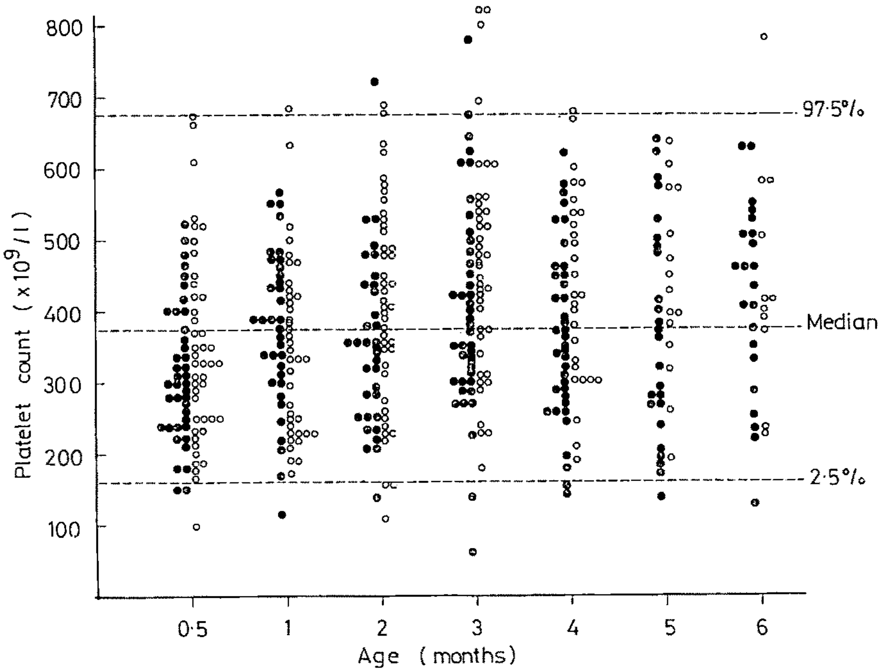

Figure *Platelet counts in low birthweight infants.* ● = *iron-supplemented,* ○ = *nonsupplemented infants. Median and 95% range of all values is shown.*

infancy and childhood, thrombocytosis is seen in connection with various rare diseases (Addiego *et al.*, 1974) of which iron deficiency and vitamin E deficiency are likely to be the most common causes in preterm babies. These results show that there were relatively high values at 2 weeks in the presence of ample iron stores. No difference was found between iron-supplemented and nonsupplemented infants. Nor were high platelet values associated with low Hb levels, except at 2 weeks. Accordingly there is no reason to suspect that a lack of iron in these infants individually, or as a group, would have resulted in thrombocytosis. Vitamin E deficiency as a cause is also unlikely as the infants were supplemented with vitamin E, and Hb levels and reticulocyte counts were similar whether their platelet counts were high or low.

The data suggest that thrombocytosis is a physiological phenomenon in preterm infants during the first 6 months of life. The increase in number might be compensatory to a decreased functional capacity shown in term infants (Corby and Schulman, 1971) and further suggests that values $<160 \times 10^9/1$ are evidence of thrombocytopenia.

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Aortography in infantile coarctation

A simple and effective technique

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SUMMARY A new and simple technique is described which clearly defines the aortic anatomy in infantile coarctation. The technique greatly helps to select those neonates whose lives can be salvaged by early surgery. There have been no serious adverse effects.

Coarctation in the neonate when associated with an interventricular septal defect or patent ductus arteriosus is a disorder which carries an extremely high mortality, in the region of 80 to 90% in the first year of life. It is usually associated with hypoplasia of the distal aortic arch and may be regarded as the mildest expression of the hypoplastic left heart syndrome.

In some cases surgery in the first months of life to relieve the coarctation and close a patent ductus arteriosus can reduce the left ventricular pressure and thus the left-to-right shunt through the residual interventricular septal defect to a tolerable level. The infant's outlook then becomes that of an uncomplicated ventricular septal defect which may even proceed to spontaneous closure. The crucial factor in improving the survival rate for infants with infantile coarctation is the selection of those infants who will benefit from early surgery. This requires adequate definition of the vascular anatomy in the area of the coarctation and has until now required arteriotomy with its inherent risk to subsequent growth of that limb, thrombosis, and many other complications. The large left-to-right shunt through an intraventricular septal defect means that left ventriculography usually provides inadequate definition of this area (Gyepes and Vincent, 1974).

Method

The use of a balloon angiocatheter floated antegradely from the pulmonary artery through the patent ductus arteriosus into the aorta permits the affected segment to be easily demonstrated (Figure). After inflating the balloon with carbon dioxide or dilute contrast medium so as to occlude the descending aorta completely, contrast is immediately injected into the aorta through the injection port proximal to the balloon and retrograde filling of the aortic arch allows cineangiograms of high quality to be obtained (Denham, 1978).

Discussion

So far this technique has been used in 12 infants and excellent angiograms have been obtained in each. There have been no adverse effects apart from transient hypertension such as often occurs after any angiogram. The precaution should be taken of using a nontoxic medium for inflation in case the balloon ruptures, and aortic occlusion should be carried out in the shortest possible time. The duration of aortic occlusion may be kept shorter than 10 seconds if carbon dioxide is used to inflate the balloon and if the angiographic injection is made by hand. Connection of the catheter to a mechanical injector and the use of dilute contrast medium for inflation both prolong the time of aortic occlusion, and for these reasons carbon dioxide inflation and manual injection are preferred.

The catheters so far used for this procedure are: No. 5 French and No. 6 French Berman Angiographic balloon catheters manufactured by American Catheter Corporation N.J. The diameter of the balloon at maximum inflation is 10 and 12 mm and

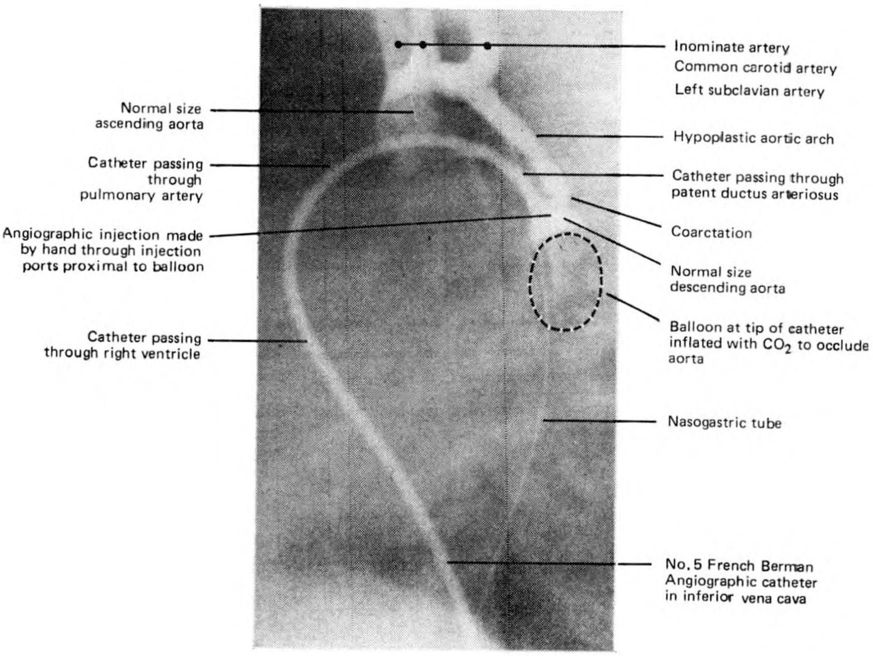
Normal size ascending aorta
Catheter passing through pulmonary artery
Angiographic injection made by hand through injection ports proximal to balloon
Catheter passing through right ventricle
Inominate artery
Common carotid artery
Left subclavian artery
Hypoplastic aortic arch
Catheter passing through patent ductus arteriosus
Coarctation
Normal size descending aorta
Balloon at tip of catheter inflated with CO_2 to occlude aorta
Nasogastric tube
No. 5 French Berman Angiographic catheter in inferior vena cava

Figure *Left lateral projection of 2·5 kg one-month-old infant.*

these catheters can therefore easily occlude the neonatal descending aorta, the internal diameter of which is 5 to 6 mm (Scammon, 1959).

This technique could be applied in other anatomic cases in which angiograms are difficult to obtain; it is particularly suitable for the neonate.

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Frequency and weight of normal stools in infancy

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SUMMARY These data give a guide to the range of stool weights and their frequency at different ages in infancy. The constancy of stool water content is emphasised.

Burkitt (1976) complained that there are no data on stool weights in normal infants. We have therefore undertaken to provide data on the variation in frequency, weight, and water content of the stools for a group of normal babies and young children fed on cows' milk formulae and mixed diets. The much looser stools of breast-fed infants prevented their inclusion in the study, because it was not possible to prevent spillage.

Materials and methods

Infants. 55 healthy infants aged between 3 days and 2 years were studied, after obtaining parental cooperation. 33 of the infants were in hospital during the study; 16 of these were aged 3–6 days (normal neonates) and the remaining 17 were in hospital for social reasons. At least 3 days were allowed for these infants to become accustomed to the hospital before collections began. The remaining 22 babies were studied in their homes. The neonates and infants under 4 months were fed *ad libitum* on proprietary milk formulae, and older infants were on a mixed diet of cereals and formula milk or unmodified cows' milk. Infants who were unwell or who had gastrointestinal symptoms were excluded.

Stool collections. Stools were collected in rayon napkin liners for 3–9 days, median 3·5. A series of *in vitro* experiments was carried out to determine whether stools collected in this way absorbed water from wet napkins or released water into dry napkins:

Effect of wet napkins
12 random stool samples weighing, with their liners, between 8·6 and 46·1 g were incubated for 2 hours in disposable napkins which had been soaked in normal saline, whose osmolality approximates that of urine. The stools and liners were then reweighed. Mean weight of stools and liners before incubation was 21·2 g, SD 11·0, and after incubation 21·0 g, SD 10·0. Mean change in stool and liner weight was −0·6%, which was not significant.

Effect of dry napkins
12 further random stool samples in liners were incubated for 2 hours in dry disposable napkins. Mean weight of stools and liners before incubation was 18·5 g, SD 8·2, and after incubation 18·1 g, SD 8·1. Mean change in stool and liner weight was −2·7%, again not significant. These findings were confirmed by detecting no significant increase in postdefecation napkin weight when stools were collected in napkin liners in infants wearing urine collection bags.

All stool collections were therefore made by this method, which proved reliable provided that the liners were properly fitted, and enabled stools to be collected at home over reasonable periods of time. At each napkin change, stool adhering to the buttocks was wiped off with the edge of the liner, and the stool and liner were then sealed in plastic bags, labelled with date and time, and frozen. Wet stool weights were subsequently measured in the laboratory, and the stools were freeze dried to determine water content.

Results

The results are shown in the Table, which divides the children arbitrarily into four age ranges. A total of

Table *Data on stool frequency, weight, and water content in normal infants at different ages*

	1st week	*8–28 days*	*1–12 months*	*13–24 months*
No. of infants	16	11	11	17
No. of stools	278	139	88	136
Stool frequency				
Mean interval between stools (hours) ±1 SD	5·2±1·9	9·9±6·5	13·2±9·2	14·9±8·3
Range (hours)	0·5–22	0·7–38·5	0·5–53	2–120
No. of stools per 24 h ± 1 SD	4±1·8	2·2±1·6	1·8±1·2	1·7±0·6
Range	1–12	0–6	0–5	0–3
Weight of individual stools (g)				
Mean	4·3	11·0	17	35
Range	0·5–48	0·3–40	2–98	4–180
Stool water content (%)				
Mean ± 1 SD	72·8±5·0	73·3±2·7	75·0±3·0	73·8±3·2
Range	65–84	72–77	72–80	66–81

641 stools were examined. As expected there was a wide range of individual variation in stool weight and frequency, but the general trend of an increase in weight and decrease in frequency with age is apparent. However, even in the second year it was common for the children to pass more than one stool a day, although some children went for 2–3 days without defecation in the absence of clinical 'constipation'. Stool water content hardly varied from the first week to the second year and had a remarkably small SD. There was no correlation between stool frequency and stool weight.

Comment

The only published information on defecation patterns in infancy is by Colón and Jacob (1977) who investigated the subject by using questionnaires. The parents in their study reported that more than half the children passed one stool daily after 18 months. These findings seem on the optimistic side for British children who on average continue to pass more than one stool per 24 hours until 2 years of age. Colón and Jacob (1977) obtained no data on stool weights.

The surprising finding in this investigation was the constancy of stool water content, apparently finely controlled to maintain an even stool consistency throughout the age range. Since stool water is easy to measure and remains so constant in health, it could be an unnecessarily neglected marker of gastrointestinal disease and deserves future study.

We intend that the range of variation in stool weight and frequency given in the Table should give some long-needed guidance for child health workers as to what constitutes 'normality'. The study also confirms the effectiveness of napkin liners.

We acknowledge the invaluable help of Mrs M. Lewis in the data collection.

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Infantile hypertrophic pyloric stenosis—unusual familial incidence

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SUMMARY A man, who had been treated for infantile hypertrophic pyloric stenosis (PS), was found to have 3 sons with the same condition. A genealogical table of his family showed that both his parents had relatives with PS. So far as it was known, none of his wife's relatives had the condition. It is suggested that the man's parents carried genes predisposing to PS and transmitted these to him in such quantity that he and all his children acquired the condition.

The aetiology of infantile hypertrophic pyloric stenosis (PS) is largely unknown. It has long been recognised that there is an increased preponderance of the condition in the relatives of patients. This familial predisposition is shown very clearly in the family to be described.

A patient (IV_4 in the Figure) had an operation at this hospital some years ago for PS. On further investigation it was found that both his brothers (IV_3 and IV_5) and his father (III_6) had been treated for the same condition. The main features of their case histories are summarised in the Table.

A genealogical table stretching over four generations was assembled for this family (Figure). The patient's mother had no known relatives with PS, but both his paternal grandfather and grandmother (II_3

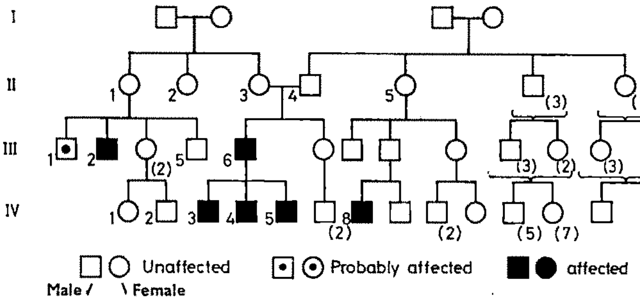

Figure *Genealogical table of family with infantile hypertrophic pyloric stenosis. Roman numerals indicate generation. Arabic numbers indicate number in generation. Figures in brackets indicate the number of unaffected individuals.*

Table *Main features of the case histories of Case III$_6$ and his 3 sons IV$_3$, IV$_4$, and IV$_5$*

Case	*Gestation at birth (weeks)*	*Start of projectile vomiting*	*Clinical findings*	*Treatment*	*Outcome*
III$_6$	40	3rd week	Case notes lost	Spasmolytics and frequent small feeds	Projectile vomiting ceased after few weeks. Uneventful recovery
IV$_3$	40	2nd day	Tumour palpated. Hypertrophy on *x*-ray	Pyloromyotomy at 4 days	Reoperated next day because of gastric retention. Diaphragm in pyloric region excised. Uneventful recovery
IV$_4$	38	3rd week	Tumour palpated. Visible peristalsis. *X*-ray normal	Pyloromyotomy at 3 weeks	Uneventful recovery
IV$_5$	40	3rd day	First *x*-ray normal. Hypertrophy on *x*-ray after 10 days	Pyloromyotomy at 2 weeks	Uneventful recovery

and II$_4$) had. Cases III$_2$ and IV$_8$ had both had pyloromyotomies performed, and III$_1$ had died on his way to hospital when he was 7 weeks, after suffering projectile vomiting and progressive weight loss from age 2 weeks.

There was no history of marriage between relatives.

Discussion

Although PS is found in infants it is not congenital in the sense that it is present at birth. The symptoms usually present between ages 3 and 6 weeks, and only rarely during the first week. All reported series show a pronounced preponderance of male to female patients, and it has long been noted that there is an increased incidence of PS in the relatives of patients who have the condition. Carter and Evans (1969) studied 813 patients treated by Ramstedt's pyloromytomy between 1920 and 1949; 20% of the sons and 7% of the daughters of their female patients had developed PS, but only 5% of the sons and 2·5% of the daughters of the male patients had developed the condition. They estimated the incidence in the general population as being 0·5% for liveborn boys and 0·1% for liveborn girls. They concluded that the hereditary background to PS is polygenic.

It would appear that there are a number of genes in different locations which may predispose for PS, and that it is necessary for a certain number of these genes to code for the condition for it to develop. The female phenotype seems to be protected to some degree so that a greater genetic load is required for girls to acquire the disease. This greater genetic load explains why the children of female patients are more likely to develop PS rather than those of male patients.

It is interesting to note that Cases IV$_3$ and IV$_5$, who were born at term, developed the symptoms at an exceptionally early age. There was little time for any postnatal environmental factors to influence the development of the condition in them. Their brother, Case IV$_4$, was born 2 weeks preterm and PS was diagnosed at age 3 weeks. All 3 brothers, therefore, developed the condition at about the same time after conception.

It is not certain from whom Cases III$_1$, III$_2$, and IV$_8$ acquired their predisposition for PS. However, finding the condition in these patients increases the likelihood of Cases II$_3$ and II$_4$ carrying genes predisposing to PS, although not to such a degree that they developed the condition. These genes were inherited by their son (Case III$_6$) in such quantity, that not only did he develop PS, but he transferred the condition to all his 3 children.

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Discontinuation of continuous positive airways pressure in infants with respiratory distress syndrome

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SUMMARY Unexpected stability of arterial oxygen and carbon dioxide tensions occurred in infants recovering from respiratory distress syndrome (RDS) on the abrupt withdrawal of CPAP at 6 cmH_2O pressure. 30 preterm infants (birthweights 880–3200 g gestational ages 29–38 weeks) were treated at a mean age of 10 hours and for a mean duration of 62 hours. CPAP was stopped when F_IO_2 requirement fell below 0·3, and stable Po_2 was maintained for 4 hours. Discontinuation of CPAP at 6 cmH_2O resulted in a mean change in Po_2 from 66 to 64 mmHg (8·8 to 8·5 kPa) and a mean change in Pco_2 from 41 to 40 mmHg (5·4 to 5·3 kPa). We conclude that this population of infants suffering from moderate RDS tolerated the abrupt withdrawal of CPAP, and that gradual reduction of pressure was unnecessary.

It is now over 7 years since CPAP was recognised as an effective mode of treatment for infants suffering from respiratory distress syndrome (RDS) (Gregory *et al.*, 1971). However there are still many unanswered questions before the maximum benefit-risk ratio is attained: the best time and mode for instituting treatment, the most efficient pressures, the techniques for monitoring complex physiological processes, and the optimal time and method for stopping treatment. With regard to this last, a prospective trial was designed to determine the effect on arterial blood–gas tensions of removing CPAP without the generally accepted weaning procedure (Llewellyn and Swyer, 1973; Krouskop *et al.*, 1975; John *et al.*, 1976; Stark and Taeusch, 1977).

Patients and methods

During the 7-month period from 1 July 1977 to 31 January 1978, 41 infants suffering from RDS were admitted to the neonatal intensive care unit. Of these infants, 30 required treatment with CPAP as the sole form of support, while 11 were treated with mechanical ventilation. The former group of infants comprised the study group.

CPAP was delivered by a nasal prong device (Wung *et al.*, 1975) at a pressure of 6 cmH_2O. This applied pressure measured at the nares was kept constant and F_IO_2 was altered throughout the course of treatment in order to maintain Po_2 in the 50–80 mmHg range. The criteria for stopping CPAP were: ambient oxygen requirement of 0·3 or less to maintain Po_2 above 50 mmHg, a stable Po_2 at this level of support for 4 hours, and the absence of clinical signs of respiratory distress. Arterial blood samples were drawn from the umbilical catheter about 20 or 30 minutes before and after the withdrawal of CPAP and measured on an IL oxygen analyser (Instrumentation Laboratories: Lexington, Mass.).

The mean birthweight of the infants was 1920 g (range 800 to 3200) and the mean gestational age 34 weeks (range 29 to 38). Nine infants weighed <1500 g, 9 were between 1500 and 2000 g, and 12 were >2000 g.

RDS was determined by *x*-ray and clinical evaluation to be of moderate severity. A-aDo_2 values were calculated at the time that treatment with CPAP was started for a precise assessment of the disease. The A-aDo_2 before treatment was 217 + 110 mmHg (mean ± SD). 70% of the A-aDo_2 values were between 100 and 300 mmHg, and 23% were between 300 and 600 mmHg.

Results

CPAP was begun at a mean age of 10 ± 10 hours (mean ± SD). The mean duration of CPAP was 62 hours, SD 36. 14 infants reached the criteria for withdrawal by 48 hours whereas the remainder required 48 to 160 hours to reach this goal.

The response of the arterial blood–gases to the removal of CPAP was evaluated at a F_IO_2 of 0·26 ± 0·04 at an A-aDo_2 of 71 ± 28 mmHg. The Po_2 on CPAP was 66 ± 9 mmHg and off CPAP it was 64 ± 10 mmHg ($P>0·5$). The Pco_2 was 41 ± 7 mmHg before CPAP withdrawal and 40 ± 8 mmHg after ($P>0·5$). The distribution of Po_2 and Pco_2 values before and after CPAP was comparable (Figure). None of the infants needed to return to CPAP after it had been stopped.

Examination of the individual responses showed that 10 Po_2 values increased and 20 decreased, while

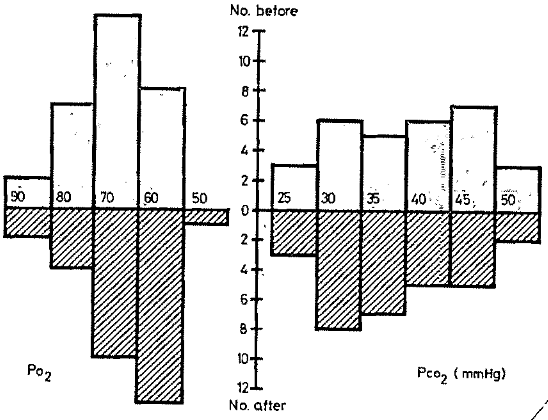

Figure *Distribution of Po_2 and Pco_2 before and after abrupt withdrawal of CPAP.*

9 Pco_2 levels increased and 18 decreased. In the data analysis a 10 mmHg change in Po_2 was assumed to be within normal limits of Po_2 variability, as suggested by observations during continuous monitoring with the transcutaneous oxygen electrode (Dangman *et al.*, 1976). Under these conditions 20 Po_2 values remained stable while 5 increased and 5 decreased. The Pco_2 before withdrawal was significantly lower in those infants in whom the Po_2 increased than in the other two groups ($P<0 \cdot 05$). A further comparison of these subgroups (Table) showed no significant differences with respect to birthweight, age at start, A-aDo_2 at start, duration of treatment, and the Pco_2 response to withdrawal.

The negative correlation between Po_2 before withdrawal and the Po_2 response remained significant in the analysis of all variables ($P<0 \cdot 05$). In addition, a significant positive correlation was noted between duration of treatment and Pco_2 before CPAP withdrawal ($P<0 \cdot 05$). No correlation was found between the Po_2 and Pco_2 responses and birthweight, gestational age, age and A-aDo_2 at the start, and F_IO_2 and A-aDo_2 at the time of CPAP removal.

Table *Comparison of the Po_2 response subgroups*

	Increased ($n = 5$)	*Unchanged* ($n = 20$)	*Decreased* ($n = 5$)
Birthweight (mean ±SD g)	2240 ± 790	1805 ± 558	2080 ± 348
Age at start (hours)	6 ± 4	10 ± 8	16 ± 16
A-aDo_2 start (mmHg)	210 ± 90	238 ± 123	197 ± 70
Po_2 prior (mmHg)	57 ± 4*	67 ± 8	76 ± 4
Change in Pco_2 (mmHg)	−4 ± 6	−1 ± 5	3 ± 4

Conversion: traditional to SI units—A-aDo_2, Po_2, and Pco_2 1 mmHg ≈ 0·133 kPa.
*$P<0 \cdot 05$.

Discussion

Before this prospective trial, the procedure for stopping CPAP in the treatment of infants with RDS had not been critically assessed, although textbooks (Llewellyn and Swyer, 1973; Pierog and Ferrara, 1976) and papers (Krouskop *et al.*, 1975; Stark and Taeusch, 1977) have suggested that weaning is the optimal method of CPAP removal.

The results of this study show that the abrupt removal of CPAP did not place any infant in a state of hypoxia or hyperoxia. The possibility that the criteria for stopping CPAP resulted in some infants being treated longer than necessary is indicated by the correlations. The positive correlation between duration and Pco_2 before withdrawal as well as the negative one between Po_2 before withdrawal and the Po_2 response, suggest that towards the end of treatment CPAP may have had a deleterious effect. These results suggest that in some infants recovering from RDS, prolonged use of constant distending pressure can cause slight Po_2 decrease and CO_2 retention. This observation has previously been reported by Nelson *et al.* (1977). Therefore abrupt withdrawal could have been completed earlier in the course of recovery.

Several hypotheses may be considered as possible explanations for the blood-gas responses to CPAP withdrawal. The removal of a constant distending pressure may result in a new ventilation perfusion relationship or in the initiation of compensatory mechanisms by the infant.

We conclude that our population of infants recovering from moderate RDS tolerated the abrupt removal of CPAP, so that gradual reduction of pressure was unnecessary. In some infants prolonged use of CPAP had deleterious effects.

We thank Drs William Fox, Leonard Indyk, and L. Stanley James for suggestions, Mr John Kennedy for statistical analysis, and Mrs Nancy Gallo for secretarial assistance.

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Change of reference style

From January 1980, the *Archives* will change its style for citing references and will follow the number system. We are making this change in order to conform with the 'Vancouver style' of uniform requirements for manuscripts submitted to biomedical journals.

Previously the *Archives* has used the Harvard reference system. Its advantages and disadvantages compared with those of the number system have seemed evenly balanced, but the editors have been aware of the burden imposed on authors and their secretaries by the different styles which different journals require. Therefore, with the unanimous agreement of the editorial committee, we have decided to support a move whereby a large—and increasing—number of major medical journals will accept manuscripts presented in one agreed style.

The system numbers references consecutively in the order in which they are first mentioned in the text. References are identified in the text by arabic numerals. For further details see instructions to authors inside the front cover, and the references cited.[1,2]

From now onwards all manuscripts submitted should accord with the new style.

[1] International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979; **1**: 532–535.

[2] Lancet. The Vancouver style. Uniform requirements for manuscripts submitted to biomedical journals. *Lancet* 1979; **1**: 429–430.

Archives of Disease in Childhood, 1979, **54**, 725–728

Neonatal Society

Meeting held on 8 February 1979 at the Institute of Child Health, London

Prophylaxis of neonatal jaundice with maternal antipyrine treatment. L. Friedman and P. J. Lewis. Clinical Pharmacology Unit, Queen Charlotte's Maternity Hospital, London.

Neonatal jaundice is common and its incidence is thought to have increased recently. Both epidural anaesthesia and oxytocin administration during labour increase neonatal bilirubin concentrations (Friedman *et al.*, 1978). Neonatal jaundice results from immaturity of the hepatic enzyme system which glucuronates bilirubin. Glucuronidation may be induced in the fetus by exposure to inducing agents and phenobarbitone treatment of pregnant women has been shown to be effective in reducing neonatal jaundice. However, phenobarbitone is sedative and rarely used. Antipyrine, an antipyretic known to induce glucuronyl transferase in adults, is without sedative properties (Orme *et al.*, 1974).

Pregnant women were recruited during the 38th week of pregnancy and allocated at random and double blind to placebo or antipyrine (300 mg daily). Babies who satisfied the protocol were seen on the 4th day after birth and total serum bilirubin concentrations measured.

90 women were recruited; 48 completed the protocol, 24 in each group. The mean (± SEM) bilirubin concentration was $111\cdot5 \pm 13\cdot5$ µmol/l ($6\cdot5 \pm 0\cdot8$ mg/100 ml) on placebo and $62\cdot6 \pm 11\cdot2$ µmol/l ($3\cdot7 \pm 0\cdot6$ mg/100 ml) on antipyrine ($P<0\cdot005$). The mean birthweights were 3·419 kg on placebo and 3·432 kg on antipyrine. Mothers in both groups took an average of 15·5 tablets. No adverse effects were noted.

We suggest that brief perinatal exposure of the mature fetus to antipyrine reduces neonatal bilirubin concentrations. The mechanism is presumed to be induction of glucuronyl transferase in the fetal liver.

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Follow-up study of babies exposed to betamethasone before birth. A. M. Butterfill and D. R. Harvey. Queen Charlotte's Maternity Hospital, London.

It has been shown that glucocorticoids given to mothers in premature labour can reduce the incidence of respiratory distress syndrome (RDS) in their babies, but animal experiments suggest that glucocorticoids may have adverse effects on growth and mental development which could outweigh the benefits. We therefore attempted to study the growth and development of 120 babies born during a controlled trial in which mothers in premature labour (at 26–37 weeks' gestation) received either betamethasone (4 mg 8-hourly × 6) or a placebo.

12 babies died, 6 from each group, and 3 were not traced. Limited information was available about 17 babies; one from the betamethasone group was severely retarded, but the others were thought to be normal. The remaining 88 children were examined once, in detail, between ages one and 4 years. The two groups (41 whose mothers received betamethasone and 47 controls) were well-matched for length of gestation (26–42 weeks), socioeconomic group, age at follow-up, and other perinatal and social factors which could affect development. There were 5 cases of RDS in the betamethasone group and 8 in the controls. At follow-up no child was developmentally retarded or suffered major handicap. Minor abnormalities and defects of vision and hearing were present equally in the two groups. There was no difference between the groups in height and weight. There was no difference in the general quotient of the Griffiths's Mental Development Scales, but the betamethasone group had lower scores on the performance scale (106, control 113, $P = 0\cdot05$).

Neurological examination of children who were small-for-dates babies. D. R. Harvey and S. M. Wallis. Queen Charlotte's Maternity Hospital, London.

Small-for-dates babies are more likely to have neurological abnormalities and learning problems in childhood than babies of normal birthweights (Dobbing *et al.*, 1971). There is evidence that animals are clumsy if their brain growth is impaired during a phase of development equivalent to that of the human brain in the latter half of pregnancy (Fitzhardinge and Steven, 1972; Neligan *et al.*, 1976).

We followed up a group of small-for-dates babies whose antenatal growth was documented with serial ultrasonic cephalometry. All were term, singleton births, with no significant neonatal problems. 20 of the children were selected for study; 10 had slow head growth starting before 26 weeks' menstrual age, and 10 had normal head growth before birth. The groups were matched for age and sex. They were seen at a mean age of 6 years and examined for evidence of minor neurological dysfunction using the technique described by Touwen and Prechtl (1970). Those children whose head growth began to slow before 26 weeks' menstrual age, had lower overall scores on neurological examination with impairment of co-ordination and balance. They also performed poorly in a test constructing matchstick shapes.

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The effects of feeding, asphyxia, and hypoxia on the oxygen tension of cerebral venous blood. R. M. Gardiner. Physiological Laboratory, University of Cambridge.

Validation of oesophageal balloon measurements in infants. C. S. Beardsmore, P. Helms, and J. Stocks. Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, and Respiratory Unit, The Hospital for Sick Children, London.

Oesophageal balloons are often used to measure transpulmonary pressure changes in infants in order to calculate their pulmonary resistance (Rp) and dynamic compliance ($C_L$dyn). In adults, numerous problems associated with the use of oesophageal balloons have been reported, but little work has been done to validate the use of this technique in infants (Dinwiddie and Russell, 1972; Milner *et al.*, 1978). Previous work shows that measurements of Rp are considerably less accurate and less reproducible than those of airways resistance (Raw) measured by plethysmography (Stocks, 1977).

In an attempt to determine why these discrepancies occur, we performed detailed *in vitro* and *in vivo* experiments to assess which factor might affect the reliability of oesophageal balloon recordings. Variations in the dimensions, wall thickness, and volume of air within the balloons were all found to affect critically their pressure volume characteristics. These factors caused significant variations in the measured values of Rp and C_L obtained from individual babies.

Recommendations are made for the ideal internal working volume and physical characteristics of oesophageal balloons for the measurement of transpulmonary pressure changes in infants.

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Effect of nasogastric tubes on nasal resistance during infancy. J. Stocks. Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London. To be published in full in the *Archives*, 1980, **55**, in press.

Blood pressure in the first 6 weeks of life. A. Earley, P. Fayers, and M. de Swiet. Department of Paediatrics, Cardiothoracic Institute, and MRC Tuberculosis and Chest Diseases Unit, Brompton Hospital, London.

Previous studies show that BP increases greatly at some time between ages 4 days and 6 weeks and then it remains constant until age 6 years (de Swiet *et al.*, 1976, 1979). However, the precise age at which this rise takes place is uncertain. Systolic BP has therefore been measured using the Parks Doppler system in 100 normal newborn infants, on alternate days during the first 10 days of life, and then at weekly intervals to age 6 weeks.

BP rose from 68 ± 11 mmHg at 2 days to 78 ± 12 mmHg at 6 weeks (after adjustment for level of consciousness). However, most of this rise (9 mmHg) took place during the first 14 days.

If, as has been suggested from animal studies (Klopfenstein and Rudolph, 1978), the cardiac output/kg body weight decreases in the first 6 weeks of life, then the concurrent rise in BP indicates that peripheral vascular resistance increases very markedly in the neonatal period.

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Congenital complete heart block in the newborn associated with maternal systemic lupus erythematosus and other connective tissue disorders. J. D. Hardy, S. Solomon, G. S. Banwell, R. Beach, V. Wright, and F. M. Howard. Departments of Paediatrics and Obstetrics, Princess Alexandra Hospital, Harlow, Department of Paediatrics, Brompton Hospital and Royal Free Hospital, London, and the Rheumatism Research Unit, School of Medicine, Leeds. Published in full in the *Archives*, 1979, **54**, 7–13.

Aspects of perinatal transcutaneous Po_2 monitoring. F. E. Hytten and M. O'Connor (introduced by I. R. McFadyen). Division of Perinatal Medicine, Clinical Research Centre, Northwick Park Hospital, Middlesex.

A preliminary series of fetal intrapartum applications of the Draeger Transoxode is reported. 23 primigravidea and 7 multiparae were studied for periods ranging from 30 minutes to 12 hours (mean 3·8 hours). Two-thirds of patients had lumbar epidural analgesia before application of the electrode at a cervical dilatation of at least 4 cm (mean 6·4).

In 9 infants, modifications to the Huch technique of intrapartum application allowed us to record fetal transcutaneous Po_2 ($FtcPo_2$) both during delivery and for a maximum of 25 minutes postnatally.

Comparisons were made between the $FtcPo_2$ and the Po_2 in fetal scalp blood samples in 26 instances, and with umbilical arterial Po_2 in 12 cases where the electrode remained in place until delivery. The correlation with Po_2 in fetal blood samples shows a mean 27·5% underestimation by the $TcPo_2$ technique. However the reliability of measuring true Pao_2 using the Saling technique must remain in doubt. The correlation with cord artery Po_2 was also poor, $TcPo_2$ values frequently underestimating systemic arterial Po_2. Factors such as local scalp circulatory stasis, the 'diving reflex', and pressure effects on the Transoxode may be responsible for the poor correlations at this stage.

Normal levels in uncomplicated labours are being evaluated. It is hoped then to proceed with correlations between $FtcPo_2$ and other parameters indicating fetal distress.

Increased concentrations of hypoxanthine and xanthine in meconium-stained amniotic fluid. R. A. Harkness, R. J. Simmonds, M. O'Connor, and F. E. Hytten. Division of Perinatal Medicine, Clinical Research Centre, Northwick Park Hospital, Middlesex.

Meconium staining of amniotic fluid is used as an indication of fetal distress. We found that concentrations of the oxypurines, hypoxanthine and xanthine, in meconium-stained amniotic fluid are generally higher than in 'normal' amniotic fluid at 38–40 weeks' gestation, both sets of samples being from patients who were not in labour. These increases cannot be directly due to meconium, since hypoxanthine and xanthine concentrations in meconium were similar to those in amniotic fluid. The concentration of urate in meconium-stained amniotic fluid was not raised and that of uridine did not show a clear increase. Serial estimations of hypoxanthine and xanthine in amniotic fluid showed that there is a tendency for concentrations to rise during labour.

The basis for this investigation was that failure to maintain intracellular ATP concentrations is associated with release of hypoxanthine into extracellular fluid. The usual cause of such failure is hypoxia. Therefore estimates of hypoxanthine in extracellular fluids could provide a cumulative measure of hypoxic damage. The increase in concentrations of hypoxanthine and xanthine in the extracellular amniotic fluid when it is meconium-stained suggests this probably occurs in the perinatal period. The results support the hypothesis that fetal hypoxia has occurred in pregnancies with meconium-stained amniotic fluid.

Studies of fetal motor activity in the 3rd trimester of pregnancy. S. Campbell, K. T. Hertogs, A. B. Roberts, and S. M. Stubbs (introduced by H. J. Shelley). Department of Obstetrics and Gynaecology, King's College Hospital, London.

Fetal motor activity was assessed by real time ultrasound scanning. All observed movements were punched directly on to computer tape. The beginning and end of each movement was recorded so as to measure the amount of time the fetus was moving in each obervation period. The number of fetal movements was also calculated and expressed as the mean/30-min observation period.

In 20 pregnant women of 32–42 weeks' gestation, the 4 components of fetal motor activity (head, trunk, arms, legs) were each computed, using two real time scanners, and correlated with the maternal subjective assessment of fetal activity. It was established that fetal trunk movements (FTM) correlated strongly with total fetal motor activity, especially in those movements described as major. Thus FTM could be used to establish normal parameters of fetal motor activity in the 3rd trimester.

In 21 normal pregnancies 24-hour profiles were obtained, by recording for 1 hour in 3, providing a total of 168 hours for analysis. The mean percentage incidence of FTM was 18%, with a mean of 29 moves/30-min observation period. There was a well-defined circadian variation (day/night = 16/22%) which was the reverse of that for fetal respiratory movements (day/night = 37/23%). The variation in both parameters was wide but the total activity (breathing plus FTM) rarely fell below 10% in any 30-min study period.

Cross-sectional day-time data from 100 normal pregnancies between 28 weeks' gestation and term suggest that the mean number of moves/30-min period was inversely related to gestational age, although the percentage incidence of FTM (mean ± SD = 18 ± 10%) was constant throughout the 3rd trimester.

FTM was also studied in 20 pregnancies complicated by intrauterine growth retardation and 25 pregnancies complicated by maternal diabetes mellitus. Preliminary data from the latter group suggest that maternal hypoglycaemia may stimulate fetal motor activity.

Correspondence

Epididymo-orchitis in Kawasaki disease

Sir,

We were interested to read the report by Morgan and Lynch of a case of Kawasaki disease (*Archives*, 1978, **53**, 916). We wish to report a hitherto unrecorded finding occurring during the course of this condition.

A 6-year-old boy was admitted to hospital because of a possible abscess in the left posterior cervical area. He had a pyrexia of 38·5°C. A confluent erythematous rash was present on his trunk and limbs, being more pronounced on the palms and soles. The left testis was slightly tender and enlarged. He had a strawberry tongue, and the veins of the bulbar conjunctiva were noted to be very prominent. The temperature returned to normal after 5 days and he then developed pain and swelling of the right wrist. At the same time there was a striking desquamation of the skin on the palmar aspect of his finger tips. The nail bed was not affected. The testicular tenderness which had been noted on admission became more marked during the next 3 days. Both testicle and epididymis became moderately enlarged. The skin of the scrotum was red and mildly oedematous. Symptomatic treatment only was offered, and after a week the testis and epididymis had returned to normal. At follow-up 6 weeks later no physical abnormalities were present.

This case fulfils the main criteria for diagnosis of Kawasaki disease suggested by Tanaka *et al.* (1976). There have been some less common associated findings in this condition. One of these is sterile leucocyturia, which was present in our case. It is almost certain that this is due to urethritis, as suprapubic aspiration carried out in the presence of pyuria in a number of these cases has shown normal bladder urine (Melish *et al.*, 1976). However, testicular involvement has not thus far been described. It is likely that the inflammation in our case started in the urethra and progressed via the vas to involve the epididymis and testis.

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Blood lead level survey

Sir,

In response to concern about possible lead pollution due to heavy traffic on a narrow eastern part of the A2 in Greenwich (Rochester Way) a small survey of the blood lead levels in preschool children living on or near the route was undertaken in October 1978. This concern had not been alleviated by the knowledge that an estimation of lead in air at this point, based on detailed studies of kerbside pollution from motor vehicles in 5 cities—including London, was between 2 and 4 μg/m^3, probably in the lower half of this range. The GLC guideline for air quality is 3 μg/m^3 (lead in suspension) over a 3-month period (Greater London Council, 1975). Topographical and traffic analysis showed that this road carried 35 000 slow-moving vehicles a day, 30% of them using diesel fuel, and many of them being of the heavy goods type. The widths of the carriageway and street were 8 and 24 m respectively, the flanking houses being of two storeys, and the road direction being east to west with a one in 40 upwards gradient towards the east.

41 children were chosen from health visitors' records and eventually 35 of them attended a clinic for venepuncture. One child withdrew before the test, and the test on one other child was abandoned for technical reasons. Analyses on these 33 blood samples were carried out at the department of chemical pathology at Great Ormond Street Children's Hospital. Subsequently another child, absent on holiday, gave a sample of blood which was tested at the chemical pathology department of the Brook Hospital laboratory.

The overall geometric mean of these results was 16·3 μg/100 ml, on a near-normal distribution, the highest reading recorded being 26·9 μg/100 ml. The normal reference range of the EEC directive on biological screening for lead is 0·3–1·8 mmol/l (approximately 6 to 37 μg/100 ml) and by this standard the levels were considered to be satisfactory. It is of interest that this mean differs only slightly from the mean of 15 μg/100 ml used by the Environment Protection Agency in the United States for setting a national ambient air quality standard for lead (final results and proposed rule making, October 1978).

There are slight variations near the mean for the subgroups and these are set out in the Table, the actual numbers being given in parentheses for each group.

These results have been interpreted as natural variations without any pattern or relationship to age, site, or residence, and there is no suggestion of statistical significance about them. There is an overlap of the 95% confidence limits for another value between the various groups in the Table. The children had lived on Rochester Way long enough to have absorbed any lead from vehicle exhausts and for it to have been fully reflected in their blood lead readings. There was no evidence of ill health attributable to the ingestion of lead among the children examined by the medical officer at the school. It was concluded that, whatever undesirable effects of traffic there may be on Rochester Way, the inclusion among them of lead pollution was not supported.

Table *Blood lead levels in 33 children*

Mean result (μg/100 ml)	*Average age*		*Average length of residence*	
	Years	*Months*	*Years*	*Months*
Children attending a nursery school on Rochester Way and living on Rochester Way (n = 2)				
19·7	4	8	3	1
Children attending a nursery school on Rochester Way and living off Rochester Way (n = 4)				
17·2	4	11	4	5
Children living on Rochester Way west of Well Hall roundabout (n = 11)				
17·6	3	3	2	5
Children living on Rochester Way east of Well Hall roundabout† *(n = 11)*				
15·1	2	5	2	3
*Children living near Rochester Way (n = 5)**				
17·8	2	7	2	5

*The child (aged 6 years) tested at the Brook Hospital laboratory, living near Rochester Way, had a blood level of 18·6 μg/100 ml.

†8 of these children lived on the narrow part of the road and their mean result was 15·1 μg/100 ml, their average age being 2 years 7 months with an average length of residence of 2 years 4 months.

Not far away, preschool children in another recent survey carried out near a lead smelter were found to have a mean level of 21 μg/100 ml (Millar, 1978).

It is important at this present time to be clear about the biological relationships with lead in the environment. Lead at low levels in blood is being associated with malfunctions which on the evidence are as likely to have other parallel and independent associations. At these levels blood lead variations would reflect environmental variations and all the differences could be significant, yet without dysfunction of any kind, or with dysfunctions otherwise explained. On the other hand, the practice of environmental evaluation and lead hazard abatement near and above the upper end of the EEC reference range is clearly indicated (Center for Disease Control, 1978).

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Cefuroxime plasma and CSF levels in children with meningitis

Sir,

Kuzemko and Walker recently reported their experience with cefuroxime in meningitis (*Archives*, 1979, **54**, 235).

We gave cefuroxime to 17 patients aged between one month and 10 years. Six of them had meningitis, the others had severe pneumonia or laryngitis. The patients with meningitis were initially treated with ampicillin, chloramphenicol, or a combination of ampicillin and gentamicin. Cefuroxime was given before the final lumbar puncture when the patient had recovered, generally after 8 days of treatment. Cefuroxime 25 mg/kg was given intravenously by 30-min infusion every 6 hours. The organisms responsible for the meningitis in 3 patients were *Neisseria meningitidis*, *Haemophilus influenzae*, and *Klebsiella pneumoniae*. In the other 3 patients with meningitis the organism could not be identified because the patients had been treated with antibiotics before admission to hospital. In the patient with *N.meningitidis*, the MIC for cefuroxime was <0·03 μg/ml. Lumbar puncture was performed 30 to 120 minutes after the end of the infusion by which time the child had received cefuroxime treatment for 24 hours. At that time, blood samples were taken 4 or 5 times from 30 to 180 minutes after the end of the infusion by an indwelling IV catheter at a site different from that of the infusion.

The resistance of *Klebsiella* to other antibiotics in a child with ventriculitis and meningomyelocele led to treatment being increased from 25 mg cefuroxime every 4 hours to 50 mg every 4 hours. The presence of an indwelling intraventricular reservoir allowed the level of the drug to be estimated in the ventricular fluid after the intravenous administration, and later after parenteral and 10 mg intraventricular administration.

All samples were assayed biologically. Adequate plasma cefuroxime concentrations ranging from 23 to 115 μg/ml were obtained throughout. The concentration in the spinal fluid (Figure) ranged from 0·2 to 1·2 μg/ml with a dosage of 25 mg/kg 6-hourly. In the child with ventriculitis, ventricular fluid concentrations were between 3·6 to 7·6 μg/ml with 25 mg/kg 4-hourly, and 16·8 μg/ml with 50 mg/kg 4-hourly; intraventricular administration resulted in very high concentrations of 26 μg/ml on the left side and 89 μg/ml on the right. The higher values found in the patient with ventriculitis are presumably due to the better penetration of the drug through the inflamed meninges. No toxic side effects were observed. These results corroborate the findings of Kuzemko and Walker.

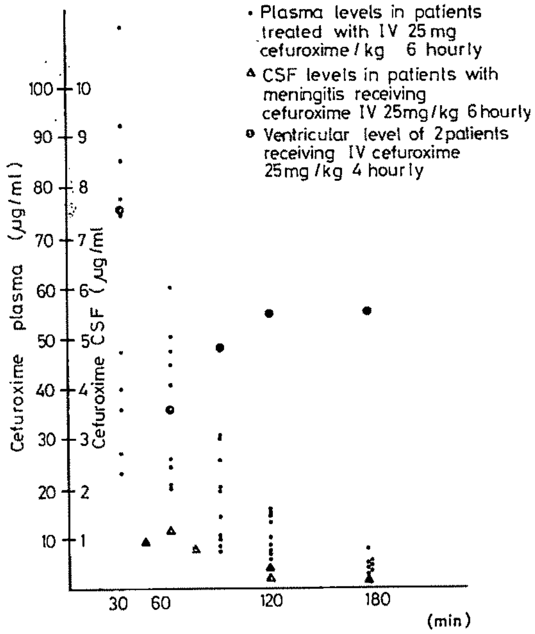

Figure *Plasma and CSF levels of cefuroxime (min) in children with meningitis or other infections.*

A cefuroxime dosage of at least 25 mg/kg 4-hourly seems suitable and should be adapted according to the MIC of the micro-organism and the level of the drug in the CSF.

We thank Mr W. Ryngaert of Glaxo, Belgium for the cefuroxime supply.

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ook reviews

etus into Man: Physical Growth from onception to Maturity. By J. M. Tanner. p. 250; illustrated + tables. £7·95 hard-ck, £4·50 paperback.) Open Books: ondon. 1978.

o describe the physical growth and evelopment of children in a manner that stimulating to the biologist and the non-chnical general reader alike, must have een a difficult undertaking but the author as succeeded magnificently. The subject atter is at the crossroads of many isciplines, thus requiring a broadly-based pproach. There are chapters not only on tal growth, sexual differentiation, the rowth curve and puberty, but also on llular mechanisms, tissue and organ rowth, and the relevant endocrinology. However, there is total coherence, and veral themes, including reference to arwinian theory, recur throughout.

Perhaps the best chapter is that on the nteraction of heredity and environment in e control of growth, for which data have een carefully selected and interestingly nalysed, with emphasis on the problem f malnutrition. For paediatricians, the hapters on puberty, early and late aturation, and standards of normal rowth, are of great practical importance; clear outline of the normal variations of ubertal development is useful. I wonered if a more specific reference should ave been made to the possible role of the ineal gland in the control of the onset of uberty, but it is inevitable that the more pecialised reader will complain that a articular section was not expanded and at he will disagree with some points of nterpretation. However, he will be ducated by finding those concepts with hich he is familiar set in a much wider ontext.

All readers will find themselves drawn rom one chapter to the next by fascinating ems of information which make the ook so readable. For example—did you now that, in one study, shorter girls more ften married men in manual jobs, that e correlation between dental and bone ge at a given chronological age is only ·4, that the shape of the human growth urve is shared only by other primates, nd that boys in certain boarding schools grew more poorly during term than in the holidays? In the closing chapters an outline is briefly given on some clinical growth disorders and, at considerable length, a 'do-it-yourself' kit is produced for parents, teachers, and health visitors to enable them to estimate the ultimate height of a child and to determine whether growth is normal. Once more the author attempts, for the best of reasons, to seduce us from the Gregorian to the Tannerian decimal calendar!

It is a short book of some 250 pages, tightly argued, lucidly written, comprehensively illustrated, and with an excellent bibliography. Professor Tanner, uniquely qualified to write such a book by the outstanding contributions he has made to the study of human growth and to child health, has produced an account which is compulsive reading for the paediatrician and which should be compulsory reading for the medical student.

D. A. PRICE

Human Growth: volume 1, Principles and Prenatal Growth; volume 2, Postnatal Growth. Edited by F. Falkner and J. M. Tanner. (Pp. 634 each volume; illustrated + tables. £24·75 each volume, hardback.) Baillière Tindall: London. 1979.

These are the first two volumes of a 3-volume comprehensive textbook about human growth from conception to adult life edited by 2 well-known authorities, one from each side of the Atlantic. Of the 21 chapters in vol. 1, 4 are about developmental biology including changes with age in biochemical constitution and the way the body handles drugs, 3 consider the methodology of growth studies, 4 are on the genetics of biochemical, intrauterine, and postnatal growth, and the rest are about aspects of intrauterine growth including the placenta. Vol. 2 is concerned with postnatal growth. It begins with chapters on cellular growth and on measuring techniques. These are followed by chapters on the pattern and control of growth before and during puberty, and a series on the growth of individual tissues including muscle, fat, bone, and teeth. Rather surprisingly the book ends with 2 chapters about low birthweight babies.

Each chapter is written by a different author, altogether in the three volumes over 60 from 10 countries. This leads to wide variations in style and aims; some chapters are very detailed reviews with many references—for example those on biochemical development and perinatal endocrinology—while others are less comprehensive; some present new information, but a few chapters are poor, unintelligible, or boring. Although variation is good, it is a pity that some chapters do not have a summary, that some subjects —for example the effect of smoking in pregnancy and the maternal deprivation syndrome—have slipped between chapters and almost disappeared, and that the index which is large is not more comprehensive. But the books are pleasing, of reasonable size, and well produced and illustrated. As a series of essays related to growth, they are fascinating and instructive. If you want to know why the newborn hippopotamus is larger than the newborn human baby, or the effects of swimming on bone age, or the male/female ratio for lean body mass, or thousands of other facts not easy to find elsewhere, these books will help.

But are they needed? The great interest in the biology of human growth during the last decade has led to a massive increase in knowledge and there is a place for such a scholarly and detailed review of the subject for the clinician and the scientist concerned with the growing human being. Unfortunately the importance of growth makes it a subject with long tentacles and a book like this that aims to be comprehensive must be huge and expensive, and will both overlap greatly with other books dealing with the basic science of childhood and be incomplete. Nevertheless this will be a useful reference book and at least deserves a place in university and paediatric departmental libraries.

The third volume is now available and shares the strengths and weaknesses of the other. It is devoted to neurobiology, with a wide ranging series of chapters on the development of the brain and the relationship between this and behaviour; the effects of variations of nutrition upon growth;

and a final scholarly chapter on the history of growth studies.

J. M. PARKIN

Maternal Nutrition and Child Health. By D. R. Shanklin and J. Hodin. (Pp. 205; illustrated + tables. $14·75 hardback.) Thomas: Springfield. 1979.

Whether maternal nutrition during pregnancy and lactation has any effect that matters on fetal growth and postnatal development remains a subject for serious debate. No one disputes the fact that birthweights are reduced by about 10% during acute severe famine (although a fall in birth rate is more noticeable), or that maternal dietary supplementation can raise birthweights by a similar amount in chronically undernourished populations. The argument is whether it matters, and ranges between those for whom the birthweight deficit corresponds to an unimportant deprivation of the luxury of subcutaneous fat, at one extreme, and those who rather vaguely suspect that it may in some way affect brain growth and hence the intellect, at the other. Those of us in relatively affluent countries are additionally faced with the question whether the preponderance of small-for-dates babies in the less privileged social classes may be partly due to an unbalanced maternal diet as well as to smoking, teenage pregnancy, and other correlates of indigence or social delinquency. The answer is by no means clear, and becomes considerably less so when attempts are made to relate disturbances of later child behaviour to smallness-for-dates at birth in babies of undernourished mothers. The myriad of inevitable and interrelated components of poverty and undernutrition defy analysis as causal factors in the genesis of performance deficits among the child victims of such society, so that it will probably never be possible to dissect the nutritional factors away from the remainder, all of which are powerful determinants of substandard human achievement. By the same token, attending to the nutritional deficits in isolation is unlikely to resolve many problems, although some good might accrue where they are severe.

For some of our colleagues, however, the matter is not nearly so complicated. The authors of this book tell us without ambiguity that 'the relationship between nutrition, especially during the prenatal period, and child mental and physical health is demonstrated to be causal and highly correlated' (sic). Some of the studies indicate that there is less than one chance in a billion that prenatal nutrition does not influence the newborn's health and subsequent mental and physical development. In addition, they say, warming to their theme, 'neurological abnormalities, such as mental retardation, cerebral palsy, and epilepsy, which have traditionally been ascribed basically to genetics or unknown causes, are linked in large part to malnutrition during the most rapid, critical periods of development. A continuum of reproductive casualty, defined as spontaneous abortion, perinatal death, cerebral palsy, epilepsy, mental retardation, hyperkinesis/learning disabilities, and minor neurological disorders, can be caused by varying degrees of prenatal malnutrition'.

The rest of the book contains a highly selected, often misinterpreted, and tediously repetitive review of the literature; and those, like your reviewer, who have been endlessly bombarded with communications from Tom Brewer and the Society for the Protection of the Unborn through Nutrition (SPUN) in spite of begging him to desist, will not be surprised to find in the Foreword that 'the scientific studies reviewed in this work represent the basis for his efforts'. One of the authors turns out to be Executive Director of SPUN.

It would all be good knockout stuff if it were not likely to be taken seriously by the 'allied health professionals' and the senators on Brewer's mailing list, and by other influential people who are without sufficient familiarity with the subject to put the book firmly where it belongs.

JOHN DOBBING

Ultrasound in Pediatrics. Edited by M. Miskin. (Pp. 337: illustrated + tables. $29·50.) Grune and Stratton: New York. 1979.

Ultrasound provides medicine with a unique noninvasive method of investigation. Unlike other imaging techniques using *x*-rays it is without radiation hazard.

Ultrasound has made a great impact on obstetrics and it was hoped would be as useful in paediatrics. Unfortunately for children, paediatricians have been slow to accept and to press for its use. Part of the blame lies in the lack of information on the use of ultrasound in children. For this reason the publication of this book welcome. It may make those dealing w sick children aware of what may be mi ing from their own armoury of investi tions.

However the book is not enti relevant to the development of paediat ultrasound in Europe. There are obvio regional differences in the definition paediatrics. European doctors might r accept alcoholic pancreatitis and caesare section scar haematomas as being partic larly paediatric problems.

Half of the book is devoted to a fasc ating account of cranial ultrasound whi is compared with pneumoencepha graphy. The authors are obviously ve experienced but computerised axial tom graphy has now become so well establish as the method of cranial examination th the lack of comparison of ultrasound w CAT will leave readers sceptical of value.

There follows a short, useful, we referenced introduction to echocardi graphy, but with only a passing comme on real time scanning.

Almost one-third of the book is left cover the abdomen and pelvis. Consideri the experience and reputation of t authors, the images are only medioc the text contains many factual errors a is not critical enough of the relative u fulness of ultrasound. However, t '*Reader's Digest* style' makes it an ea introduction to this topic and interesti reading despite the irrelevancies a errors.

C. METREVEI

Shorter notice

Smith's Blood Diseases of Infancy a Childhood, fourth edition. Edited D. R. Miller, H. A. Pearson, R. Baehner, and C. W. McMillan. (Pp. 88 illustrated + tables. £34·00 hardback Mosby: St Louis. 1978.

The original textbook of pediatric haem tology has, inevitably, in this, its 4 edition become a multiauthor book. T editors manage to combine basic physi logy (for example of erythropoiesis ar haemolysis) with comprehensive clinic coverage (as in the excellent chapter iron metabolism). The result is surprising readable and up to date and, despite t price, must be the best buy for a depar mental library.

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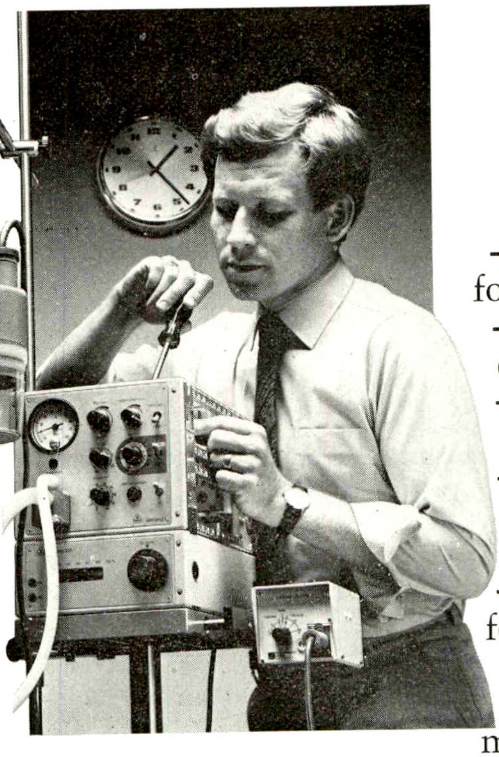

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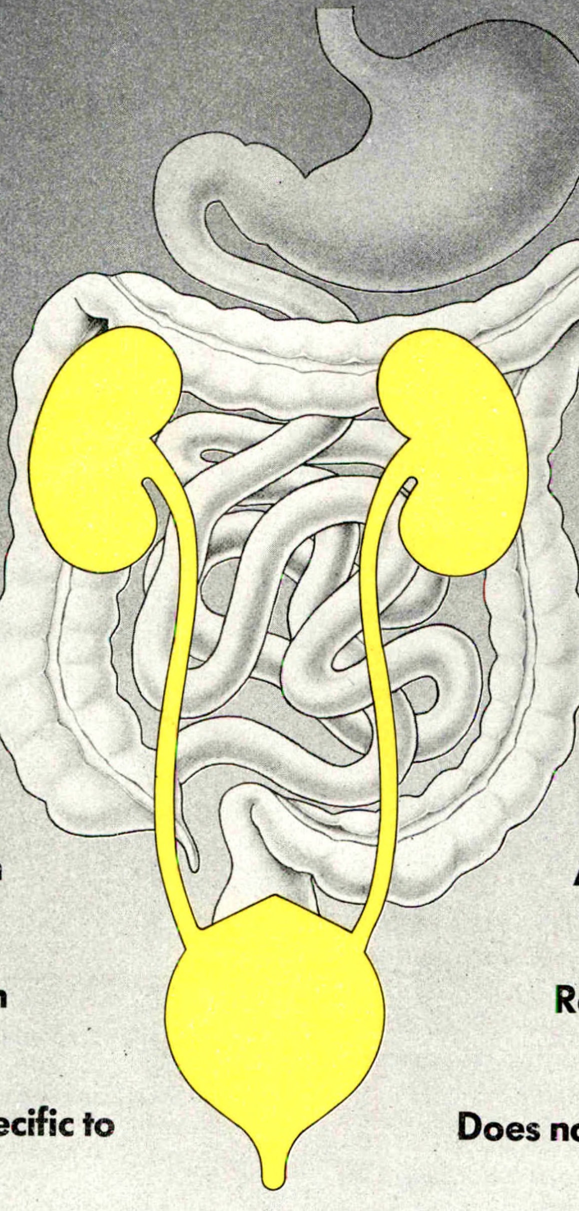

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Archives of Disease in Childhood, 1979, **54**, 733–734

Annotation

Human growth hormone (UK)

Human growth hormone manufactured in the United Kingdom (GH (UK)) has been available since 1959 for the treatment of patients suffering from growth hormone deficiency. At that time a Working Party of the Pituitary Hormone Committee of the MRC was formed to design and carry out a clinical trial of GH (UK) as a growth promoting agent in patients of short stature. Favourable therapeutic results led to extension of the trial from simple assessment of the efficacy of GH (UK) to more detailed studies of the best mode of usage. From being a purely research exercise in the early 1960s the emphasis of the Working Party's remit shifted gradually to a service commitment to provide GH treatment for those who need and can benefit from it. This led to the development of a national system for the evaluation and treatment of patients suffering from lack of GH and in 1977 responsibility for the provision of treatment with GH (UK) transferred from the MRC to the DHSS. The experience accrued by the MRC Working Party has recently been published.[1] A Health Services Human Growth Hormone Committee (HSHGHC) was created by the DHSS to replace the MRC Working Party and in announcing this the department commented[2] '. . .The demand for hGH and the supply from pituitaries are fairly finely balanced and are expected to continue to be so in future. . . .It is likely that treatment with hGH will for some years be regarded as a new and developing service and paediatricians with experience and expertise in this specialised area will tend to be those who have been associated with the MRC trial and the growth assessment centres. Moreover, given the limited availability of hGH it is important that broadly uniform clinical criteria are applied in the selection of patients and the determination of therapeutic regimens.'

Today there are 19 growth assessment centres in the UK at which patients are measured and the effects of treatment monitored. Allocation of GH (UK) is decided by the HSHGHC quarterly on the basis of application by the physician in charge of the patient. An integral part of the application is the anthropometric information provided by the growth assessment centre. The HSHGHC has a co-ordinator who is responsible for collating information from the centres and sending GH (UK) to them for distribution to the patients.

GH (UK) has been extracted at the Department of Biochemistry, University of Cambridge since the beginning of the MRC trial using acetone-preserved pituitary glands as starting material. The GH (UK) prepared in this way has been shown to be therapeutically effective and free from side effects over 17 years with the exception of a few patients (less than 2%) who develop growth inhibiting antibodies. The preparation is known not to be homogenous protein and to contain large molecular weight components inferred to be aggregated GH and small but detectable concentrations of other pituitary hormones when tested by immunoassay.[1] Other methods of pituitary preservation and growth hormone extraction have been studied in an attempt to obtain a purer product. GH (UK) has been prepared from frozen glands at St Bartholomew's Hospital, London and used successfully in the treatment of certain patients who had developed growth inhibiting antibodies to conventional therapy with GH (UK). Commercial therapeutic GH is also prepared from frozen glands. The relative advantage of preserving pituitary glands in acetone or by freezing is not obvious. Freezing is less damaging to the peptide hormones in the pituitary but may also result in the preservation of other contaminants among which viruses are a remote but particular cause of concern. The logistics of preserving and transporting frozen glands nationally is more difficult than for acetone-preserved glands. After considering all the factors carefully, the department has made plans for the future production of GH (UK), initially from acetone-preserved glands using a modified extraction procedure which includes additional steps to remove high molecular weight aggregated and contaminating hormones. Arrangements have been made to transfer production to the Centre for Applied Microbiological Research at Porton Down which should begin to supply GH (UK) at the end of 1979. A research and development programme will operate concurrently at Porton which will include other methods of production.

An important argument against using GH from commercial sources overseas is cost, but even more important is the question of supply. Industry could not provide the quantity of GH needed in the UK from existing stocks and would have to rely on the provision of pituitaries collected in the UK for hormone extraction. The processing of the glands by the companies could take place in the UK or in Scandinavia, but in either event would raise ethical and legal questions since a Council of Europe resolution,[3] accepted by the UK forbids the offering of substances (human material or extracts of such material) for profit. Finally if the glands were to pass out of our hands there could be difficulty in ensuring the return of *all* extracts from them. All the GH that can be extracted from UK pituitaries is needed for therapeutic purposes in the UK and other extracts from the glands have important research and commercial potential.

Recently it has been alleged that: 'hGH (UK) currently in use or an impurity in it accelerates osseous maturation either via thyroid or gonadal stimulation to a greater degree than it increases linear growth with the result that ultimate short stature (in most cases <3rd centile) is likely to result from the treatment of patients with short stature with hGH (UK)'.[4] This communication was delivered to the annual meeting of the BPA in York on 28 March 1979. The next day an article appeared in the *Glasgow Herald* headed 'HGH "Wonder cure" has turned sour for our poor growth youngsters'.[5]

The communication and the associated publicity were completely contrary to the published experience of the trial,[6] but in view of the distress caused to patients, their parents, and to the parents of potential patients, a new and detailed review of all patients treated with GH (UK) for whom bone age and height records are available was carried out.[7] Of 215 patients, 122 had isolated growth hormone deficiency, 63 had a deficiency of one or more pituitary hormones (panhypopituitarism), and 30 had a craniopharyngioma. Patients with craniopharyngioma or panhypopituitarism were treated with other hormones that could accelerate osseous maturation in addition to growth hormone. The duration of treatment varied from one to 13 years but since there was no relation between the time on treatment and rate of bone maturation it was possible to consider all cases together. The overall mean bone age velocity of patients with isolated growth hormone deficiency and panhypopituitarism was 1·00 and 0·97 bone age years respectively, but that of patients with craniopharyngioma was less: 0·57. These results show that treatment with GH (UK) does not cause pathologically accelerated bone maturation. To compare the growth in height with bone development it was necessary to calculate the height standard deviation score for bone age.[6] If osseous maturation is stimulated by GH (UK) to a greater degree than linear growth as alleged[4] then the height SD for bone age will become lower (that is more negative) as a result of treatment. In fact the opposite was observed in patients with craniopharyngioma and isolated growth hormone deficiency. In both groups the height SDs for bone age became significantly higher as a result of GH (UK) treatment showing that therapy increased growth in bone length more than osseous maturation. In the patients with panhypopituitarism no significant change in height SDs for bone age was observed, indicating that growth in height and osseous maturation was occurring proportionately.

Growth hormone treatment is one of the outstanding therapeutic successes in recent years and all paediatricians will wish to make it available to the greatest extent that supply will allow. The nationally co-ordinated scheme that operates in the UK ensures that this objective is fulfilled for our patients.

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Congenital fibre type disproportion myopathy

A histological diagnosis with an uncertain clinical outlook

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SUMMARY Nine children with congenital fibre type disproportion (CFTD) are described. Their muscle biopsies contained type 1 fibres which were smaller than the largest type 2 fibres by at least 13·5%. Attention is drawn to the variable natural history of this disorder which generally carries a good prognosis but may sometimes be associated with fatal respiratory problems. For important therapeutic, genetic, and prognostic reasons CFTD must be distinguished from other conditions with similar histochemical or clinical features.

In 1969, Brooke and Engel reported the histographic analysis of muscle fibre types from 180 children and distinguished five separate groups of biopsies. One of these was characterised by relatively small, and sometimes excessively numerous, type 1 fibres and large type 2 fibres. Clinically the children in this group had been floppy infants whose condition generally improved as they grew older. Brooke (1973) subsequently described a further 12 cases to which he gave the name congenital fibre type dysproportion (CFTD). In the interim period other cases were recorded (Caille *et al.*, 1971; Noronha, 1973), although probably the earliest descriptions of this disorder were by Farkas-Bargeton *et al.* (1968) and Dubowitz (1969).

Since 1973 there have been a few similar reports (Fardeau *et al.*, 1975; Lenard and Goebel, 1975; Serratrice *et al.*, 1975), and Spiro *et al.* (1977) described 3 infants who died of respiratory failure all of whom had small type 1 muscle fibres.

We present a further 9 patients whose muscle biopsies showed the presence of type 1 fibres which were smaller than the largest type 2 fibres by more than 13·5%. We think that these children could be said to have CFTD and that this has important genetic and therapeutic implications which are of interest to paediatricians. We also wish to stress the difficulties of making this diagnosis and the need for further debate to delineate more fully the natural history and histochemical features of the disorder. The case histories of 2 children are given in full in order to give the range of clinical symptoms; the histories of all the children are summarised in Table 1.

Case histories

Case 1. Pregnancy was normal and there were normal intrauterine movements. The baby, a girl, was born at term by breech delivery with forceps to the aftercoming head, and weighed 2·8 kg. In the newborn period she was noted to be floppy and to have a left 'clicking' hip. There were no respiratory or feeding difficulties.

In the family history her mother had been a 'bottom shuffler'.

The child was first seen at this hospital aged 6 weeks, by which time she was smiling. On examination she was visually alert. She had a circumflex-shaped mouth but no obvious facial weakness. There was no tongue fibrillation and no fasciculatory finger movements. She was markedly hypotonic and could just move her limbs against gravity. She was areflexic. She was nursed in double nappies because of her hip.

Investigations at that time showed a CPK high on one occasion and normal on others. Electromyography of her right tibialis anterior muscle was myopathic. A muscle biopsy of her left quadriceps showed type 1 fibres which were smaller than type 2 ones (Table 1), and a small proportion (4½%) of fibres which might be considered as type 2C.

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Table 1 *Summary of some of the clinical features of 9 cases of congenital fibre type disproportion*

Case	*Sex*	*Family history*	*Delivery*	*Presenting symptoms*	*Milestones*	*Operative procedures*	*Age when last seen (years)*	*Centile*		*Other comments*
								Height	*Weight*	
1	F	Mother had weak legs in childhood: now normal	Breech: forceps to the after coming head	Hypotonia. CDH	M: Delayed Sp: Slight delay S: Normal	R. femoral osteotomy	2¼	10th	10th	See full history
2	F	Parents were 2nd cousins. Two maternal cousins 'doubled jointed'	Forceps because of toxaemia	Hypotonia. Weakness	M: Delayed Sp: Normal S: Normal	L. adduction rotation osteotomy	2¼	10th	<3rd	Contractures at 2 months. Hypermobile hand joints. Improved with age
3	M	None	Caesarean section for previous placenta previa	Weakness. CDH. Vertical R. talipes	M: Delayed Sp: Normal S: Normal	Bilateral open reduction of hips and femoral osteotomies	2	3rd	<3rd	Contractures. Hypermobile joints of hands and feet. High arched palate. Mild scoliosis
4	M	None	Normal 1st of twins	Hypotonia. Joint hyperextensibility. Weakness	M: Delayed Sp: Normal S: Normal	None	1½	50th	<3rd	Contractures. Small penis and absent testes. Normal twin sister
5	F	None	Normal	Fixed dorsiflexed position of feet. Poor sucking	M: Delayed Sp: Delayed S: Delayed	Elongation of extensor tendons	2¾	<3rd	<3rd	Improving with age
6	F	None	Elective caesarean section	Delayed motor milstones	M: Delayed Sp: Normal S: Normal	Release of R. tendo achillis	6	<3rd	<3rd	Increased weakness exacerbated by operative immobilisation. Scoliosis. High arched palate
7	F	Two paternal cousins had CDH	Breech	Hypotonia. Bilateral talipes. CDH	M: Delayed Sp: Normal S: Normal	Derotation osteotomy. L. innominate osteotomy. Posterior medial release of both feet. Bilateral extension tendo achillis	3½	10th	10th	Improving with age
8	M	None	Breech	Dyspnoea	M: Delayed Sp } Not reliably S } assessed	Tracheostomy	Died aged 1¼	15th	15th	See full history
9	F	None	Normal	Stridor. CDH	M: Delayed Sp: Normal S: Normal	Open reduction L. hip	3¼	<3rd	<3rd	Frequent chest infections, stridor improving with age

M = Motor, Sp = speech, S = social, CDH = congenital dislocation of hip.

At follow-up there was concern about the instability of her right hip which tended to sublux and at age 2 years a right varus derotation osteotomy was performed.

Although she could sit at 7 months she was still not walking alone at 2¼ years when last seen. She was reluctant to bear weight, could not pull to stand, and could take only 2 steps holding. She shuffled on her bottom. Her social responses were appropriate for her age and she had good comprehension, but her speech was confined to single words. Her height and weight were on the 10th centile.

Case 8. Pregnancy and intrauterine movements were normal. Delivery was by breech at 36 weeks and Apgar score at one minute was 8. Birthweight was 3·7 kg. There were no problems in the newborn period and the baby, a boy, sucked well. He smiled at 6 weeks.

There were no worries about him until age 4 months when during a period of 2 days he became ill with a cough and fever. On admission to hospital he was found to be dyspnoeic and to have a collapsed left lung. Within a few hours his condition deteriorated and he required high concentrations of oxygen to maintain his blood oxygen (Po_2) levels. 4 ml of pleural fluid was aspirated which later grew a coagulase-positive staphylococcus.

On transfer to this hospital 4 days later he was noted to be hypotonic with normal reflexes. Closer questioning of the parents disclosed that head raising in the prone and supine positions had always been poor. There were no cranial nerve abnormalties. There were no dysmorphic features and no skeletal abnormalities. Bronchoscopy did not show any significant abnormality. A barium swallow showed incoordinate swallowing with reflux into the posterior nasopharynx; the lowest portion of the oesophagus was dilated, and normal oesophageal stripping waves were ineffective. Pulmonary arteriography and left ventricular angiography were normal.

Six days after admission, assisted ventilation became necessary because of persistent respiratory failure secondary to left-sided collapse, and subsequently he developed a right upper lobe pneumonia and a right tension pneumothorax. 10 days after admission his liver function was first assessed and his liver enzymes were found to be raised (alanine amino transferase 150 IU/1 and aspartate amino transferase 104 IU/1). His liver edge felt firm but there was no hepatomegaly. These enzyme abnormalities gradually improved during the next months.

Three weeks after admission his CPK was estimated and found to be raised (14·6 µmol/ml per hour at 37°C, normal <3·6). In view of a recent history of intramuscular injections, the significance of this finding was uncertain. However, subsequent estimations showed a persistent abnormality and, in view of this, electromyography and muscle biopsy were performed. Sampling with a concentric needle electrode in right deltoid and vastus medialis did not show any abnormality, but his biopsy from left tibialis anterior when he was 6 months showed the presence of type 1 fibres which were smaller than the type 2 with no other abnormality (Table 2). Three months after admission, a tracheostomy was performed and he continued to require assisted ventilation until the time of his death at 14 months. Repeat contrast investigations of the upper alimentary tract confirmed that reflux into the respiratory tract continued, so that it was difficult to be certain to what degree his respiratory difficulties were a reflection of this or of his myopathy. He continued to remain very hypotonic and weak and be unable to sit alone. Two weeks before he died he developed fits which were generalised and left focal. Epilepsia partialis continua down the left side was resistant to anticonvulsant treatment. His clinical condition after the onset of these fits deteriorated rapidly and computerised axial tomography (CAT) of his brain showed pronounced cerebral, cerebellar, and brain stem atrophy. He died from bronchopneumonia and congestive cardiac failure.

Table 2 *Summary of muscle biopsy features*

Case	*Age at biopsy (months)*	*Muscle biopsied*	*Fibre types percentage*				*Fibre size (µm)*			*Percentage difference by which type 1 is smaller*	
			1	*2A*	*2B*	*2C*	*1*	*2A*	*2B*	*Than 2A*	*Than 2B*
1	2	Vastus lateralis	37·5	29	13·5	4·5	14·25±2·2	16·5±2·2	16±2·2	13·6	10·9
2	14	Vastus lateralis	51	29	20		13 ±0·15	18·5±4	19·5±4	29·7	33
3	10	Vastus lateralis	33	24	43		14·5	16·5	17·5	12·1	17·1
4	12	Vastus lateralis	44	34	22		11 ±1·7	16·5±1·7	22 ±2	33·3	50
5	18	Tibialis anterior	51·1	33	15·5		18 ±2·4	21 ±2·9	26 ±2·2	14·2	30·7
	18	Gastrocnemius	50·5	37	12·5		13·5±1·4	17 ±2·2	21·5±4·4	20·6	37·2
6	30	Vastus lateralis	50	27	23		18·6±3·6	28·7±4·8	29·4±5·4	35	36·6
7	30	Peroneus	55	31·5	13·5		28·5±6·7	40 ±4·9	43 ±4·9	28·7	33·7
8	6	Tibialis anterior	37·5	42	20·5		13·5±4	27 ±4	24·5±4	50	44·9
9	27	Vastus lateralis	52		48		7–10 µm	16–26 µm			

Normal fibre diameters are from about 14 µm at birth to about 21 µm at 2½ years.

Investigations found to be normal were: sweat test, blood viral antibody screen, absence of vacuolated lymphocytes, urine mucopolysaccharides, blood copper, and zinc. Urine amino- and organic acids on some occasions were normal and at other times showed a raised glycine and taurine and raised parahydroxyphenyllactic and parahydroxyphenylacetic acid. These abnormalities were considered to be a reflection of his impaired liver function. He was shown to have a low IgG (26 IU/ml) and a high IgM (>170 IU /ml) at 4 months. His height and weight were both on the 15th centile.

Investigations

Electromyography was performed in all but one patient. The findings suggested a myopathy in Cases 1, 3, 4, and 5, were normal in Cases 2, 8, and 9, and suggested denervation but with normal nerve conduction studies in Case 6. CPK estimations were slightly raised in Cases 4, 5, and 6, significantly raised in one (Case 8), slightly raised on one occasion and normal on another in Case 2, and normal in the others.

One (Case 5) was extensively investigated on account of her low height and weight. The following investigations were normal: sweat test, barium meal and follow through, barium enema, jejunal biopsy, duodenal enzymes on aspiration. No organism was found in the pancreatic juice although she had been treated several months previously with metronidazole for giardia infection of the gut. Her serum albumin was normal.

Other investigations which were performed and found to be normal are shown in Table 3.

A muscle biopsy was obtained in all cases and treated as described previously (Lake and Wilson, 1975). In addition, muscle tissue was obtained from some patients during the course of orthopaedic surgery. The least diameter of a minimum of 50 fibres of each type covering several muscle fascicles was measured in the acid preincubated 'ATPase' preparations using a calibrated eyepiece graticule. Most muscle fibres do not show a uniform shape and, for this reason, the minimum diameter was measured as this gives the best approximation to the true diameter regardless of the plane of section. An indication of the diameters measured is shown in Fig. 1. The mean diameter and SD for each type is shown in Table 2. The fibre type percentage is calculated from a fibre type analysis of several muscle fascicles containing at least 200 muscle fibres, using the acid preincubated 'ATPase' preparations to define the three main fibre types.

Table 3 *Investigations for which the results were normal*

Investigation	*No. of patients investigated*
Blood thyroxine	5
Thyroid stimulating hormone	1
Pyruvate and lactate	4
Urine amino- and organic acids	5*
Blood amino-acids	6
Urine mucopolysaccharides	2
Liver function tests	2†
Blood chromosome analysis	2
CAT of the skull	2
Congenital infection screen	3

*The urine of Case 8 intermittently contained raised glycine and taurine.
†Serum alanine and aspartate aminotransferase levels were raised in Case 8.

Muscle tissue was obtained at necropsy from Case 8 and frozen for cryostat sectioning. Samples were taken from left and right tibialis anterior, vastus lateralis, psoas, diaphragm, rectus abdominis, sternomastoid, biceps brachialis, sartorius, and trapezius.

Pathology

The only change noted in each of the (*in vivo*) biopsies was a disproportion in size of type 1 and type 2 fibres. There was no increase in numbers of central nuclei, endomysial connective tissue, degeneration, or other nonspecific features associated with denervating or myopathic conditions. The more specific features of nemaline myopathy or central core disease were not seen. In one biopsy (Case 7) many of the type 1 fibres showed 'motheaten' characteristics.

The disproportion of the size of type 1 and the largest type 2 fibres (Table 2) was always greater than 13·5% and in 7 out of 9 patients the 2B fibres were larger than the 2A ones. The proportion and size of type 1 fibres were in most cases within the normal range. The coefficient of variability of the type 2 fibres was less than 250 in all patients.

In Cases 2 and 9 a biopsy of sartorius taken during reduction of the dislocated hips did not show disproportion of fibre diameters, although biopsies of vastus lateralis taken earlier (Case 9), or later (Case 2), showed the characteristic disproportion.

The muscles sampled at necropsy of Case 8 showed pronounced intersample differences and had changed remarkably since the biopsy taken at age 6 months. In each muscle examined from this patient there was an increase in endomysial connective tissue, a greater number of central nuclei, and pronounced variation in fibre diameters which did not correlate with fibre type. Cytoplasmic bodies, staining bright red in the trichrome preparations, were present even in the more mildly affected muscles. Considerable infiltration by histiocytes showing acid phosphatase activity was noted with only little evidence of regenerative changes although some of the central nuclei were plump and occasionally several were present in one fibre. The degree of involvement could be roughly graded from the least affected muscle to the most affected in the following order: tibialis anterior, sternomastoid, sartorius, biceps brachialis, psoas, rectus abdominis, vastus lateralis, trapezius, and diaphragm. In Figs 1–4 the biopsy findings are compared with those found at necropsy.

The lungs showed bronchopneumonic changes and some hyaline membrane formation. Other tissues appeared normal or showed only slight changes. In particular there was no evidence of any abnormality of anterior horn cells, nor was there evidence of storage disease.

Discussion

Some of the clinical features of our 9 cases are shown in Table 1. A family history of neuromuscular problems was present in only 2 children (Cases 2 and 7); in one the parents were second cousins and two maternal cousins were said to be 'double jointed', and in the other case two paternal cousins had had CDH but no other neuromuscular problems. Six of the 9 patients were girls.

Pregnancy was normal in all but one instance in which there was terminal toxaemia, and intrauterine movements were experienced normally by all mothers.

Delivery was complicated in 6 out of 9 patients: Cases 1, 7, and 8 were breech presentations, Cases 3 and 6 were caesarean sections, one electively and the other for placenta praevia, and foreceps was used in Case 2.

Generalised hypotonia and weakness were noted early in 6 children and became evident within the subsequent 2 years in the remaining 3 (Cases 5, 6, 9) although in Cases 5 and 9 these symptoms were only slight. There was no significant deterioration in any patient after age 2 years and in 3 there was greater improvement in strength than might have been anticipated from natural maturation alone.

Respiratory difficulties were present in the newborn period in only one child (Case 9) who had laryngeal stridor. One other patient (Case 5) sucked poorly.

Congenital dislocation of the hip was noted in about one-third of our cases. Other skeletal abnormalities were not uncommon and included deformities of the feet in 3 children (Cases 3, 5, and 7), scoliosis and high arched palate in Cases 3 and 6. Cases 2, 4, and 8 had no skeletal deformities. Muscle contractures commonly developed and reflexes were depressed or absent. Height and weight tended to be about or below the 3rd centile in most instances. Motor milestones were delayed in all patients, but speech and social development was normal in all except Cases 1 and 5.

These clinical features are very like those described by Brooke and Engel (1969) and Brooke (1973) in the majority of their patients. In their series there was a slight preponderance of females, and in ours there were twice as many females as males, but the numbers are too small to form any valid conclusions. Delivery was complicated in 6 out of our 9 cases whereas it was normal in all but 2 of Brooke and Engel's cases. Half their patients had high arched palates whereas this was a feature in only 2 of ours. Brooke commented that recurrent respiratory infections 'may be a problem'. This was true of Case 9 in our series, and in Case 8 the clinical picture was dominated from age 4 months onwards by persisting and very severe respiratory difficulties necessitating continued assisted ventilation. This child is reminiscent of those described by Spiro *et al.* (1977) and leads us to confirm their impression that respiratory failure is a rare but definite feature in CFTD.

Although the clinical features of CFTD are distinctive they are by no means exclusively diagnostic and may also be present in several other congenital myopathies—such as nemaline myopathy and infantile myotonic dystrophy. A disproportion in fibre sizes, type 1 fibres being smaller than type 2, may also be present in these two conditions with the result that it may be difficult to distinguish them one from another and from CFTD. This difficulty is illustrated by the report of Caille *et al.* (1971) where it is clear that their Case 1 had CFTD and their Case 2 nemaline myopathy.

None of the biopsies of our patients contained nemaline rods whereas they were present in 2 of the cases of Brooke and Engel (1969), and it is interesting that these 2 patients had very high arched palates—a feature characteristic of nemaline myopathy. We feel that these patients could more properly be said to have had nemaline myopathy. Although we recognise that nemaline bodies may be found in a variety of conditions (Dubowitz and Brooke, 1973) and that therefore the presence of such bodies does not necessarily imply the diagnosis of nemaline myopathy, nevertheless it would appear to us more logical to call the association of nemaline bodies and type 1 fibre atrophy, nemaline myopathy, than to attempt to extend the histochemical picture of CFTD to include the presence of nemaline bodies.

The distinction between CFTD and neonatal myotonic dystrophy may be difficult on both histochemical and clinical grounds in the early stages. However in over 90% of cases of neonatal myotonic dystrophy, myotonia can be clinically

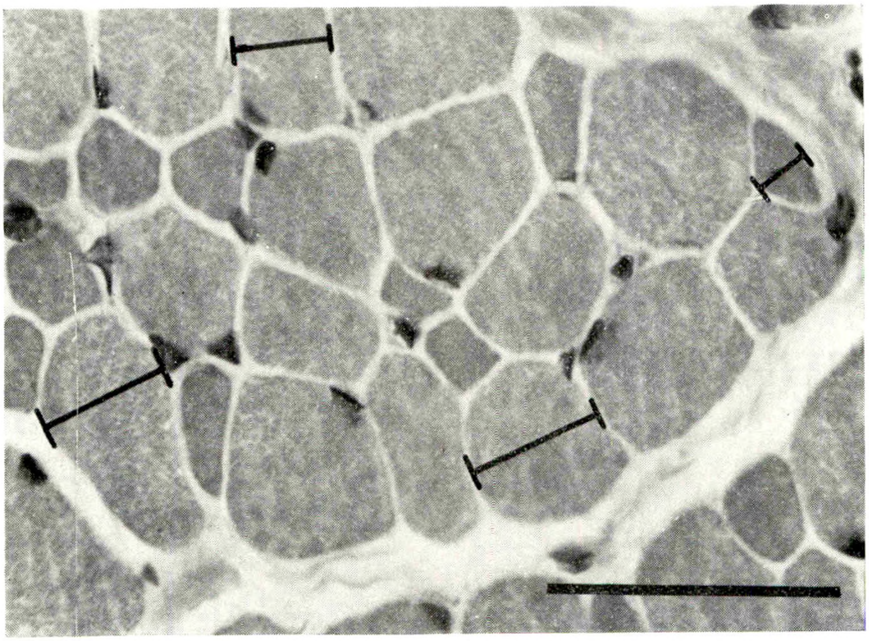

Fig. 1 *Biopsy of L. tibialis anterior at 6 months (Case 8). Haematoxylin and eosin preparation showing two populations of fibres without other myopathic features. An indication of the fibre diameters measured is also shown for four fibres. Scale mark 50 μm. × 700*

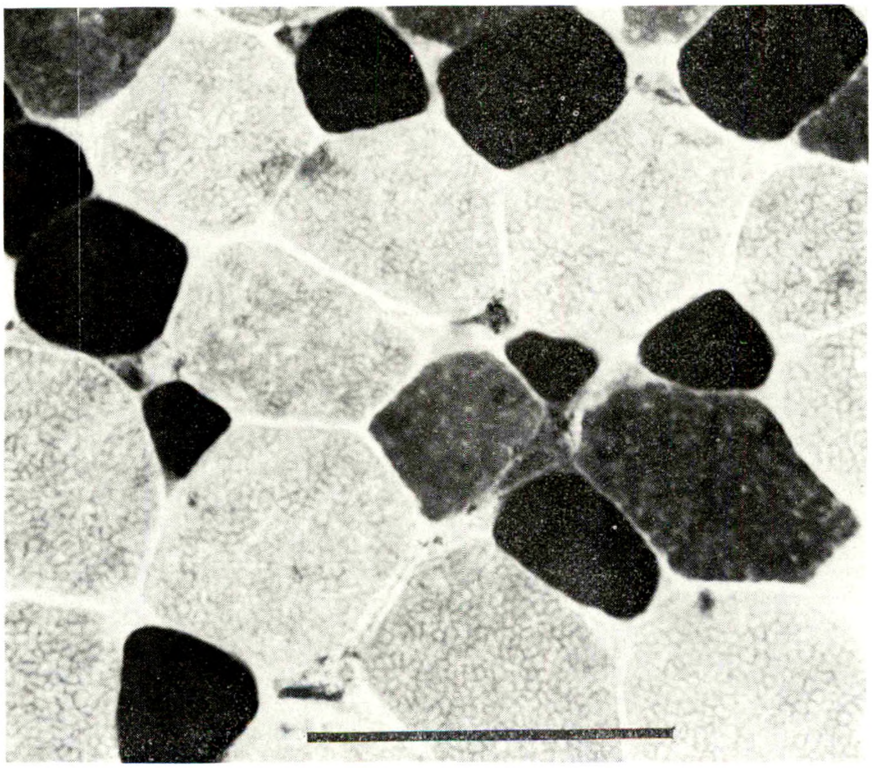

Fig. 2 *Biopsy L. tibialis anterior (Case 8). 'ATPase' preparation after preincubation at pH 4·3 showing that the small fibres are all of type 1. Scale mark 50 μm. × 950*

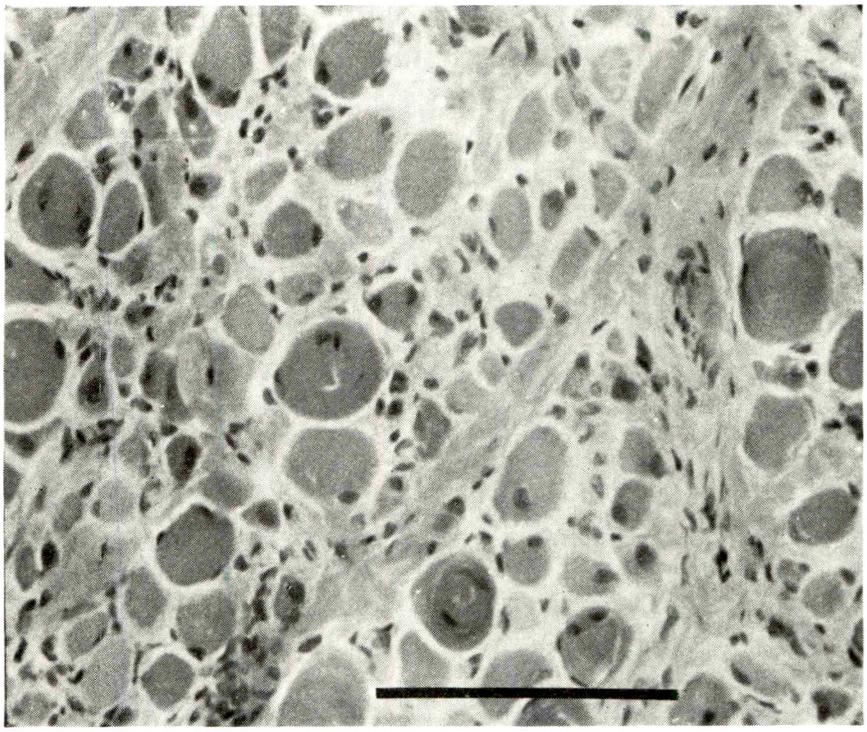

Fig. 3 *Necropsy diaphragm muscle (Case 8). Haematoxylin and eosin preparation showing pronounced variation in diameter of fibres, increase in connective tissue, central nuclei, and whorled fibres. Scale mark 200 μm. × 200.*

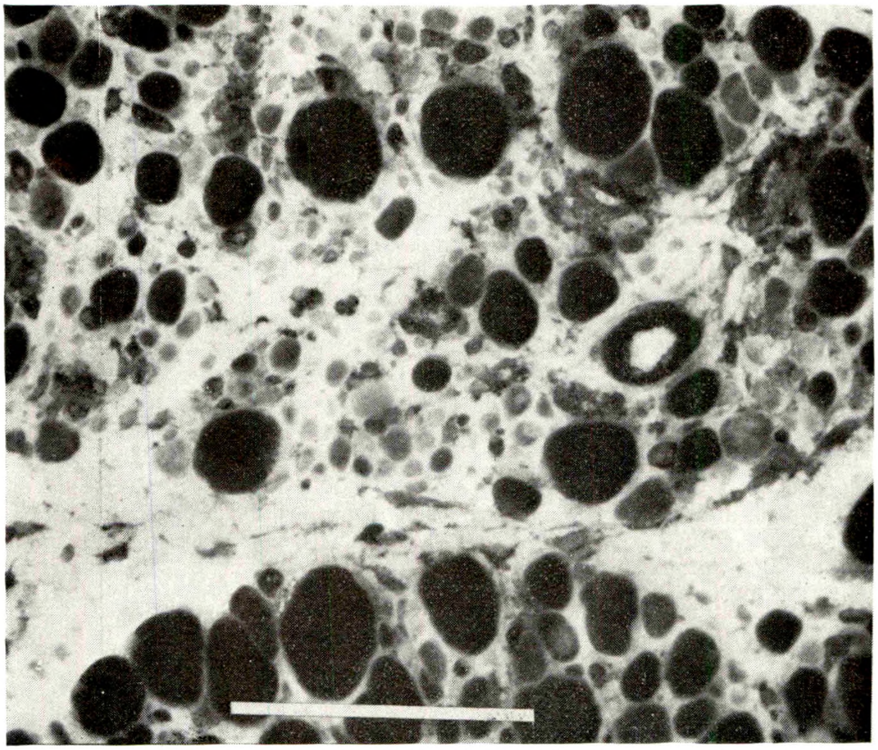

Fig. 4 *Necropsy trapezius muscle (Case 8). 'ATPase' preparation after preincubation at pH 4·3 showing that the orderly pattern of the biopsy (Fig. 2) has been replaced and that the large fibres are now mainly type 1. Scale mark 100 μm × 400*

elicited in the mother. None of the mothers of our cases had myotonia.

The significance of the presence of 'motheaten' type 1 fibres in Case 7 is uncertain, but it is interesting that this patient was the only one in whom bilateral talipes equinovarus was present; this association was reported previously by Dubowitz and Sharrard (1968).

The absence of fibre type disproportion in sartorius muscle in 2 patients confirms the impression of Spiro *et al.* (1977) that there may be 'striking intersample differences', and this is also seen in the marked differences between the muscles sampled at necropsy of Case 8.

The appearances of the muscle at necropsy in Case 8 are very similar to those of congenital muscular dystrophy and it could be speculated that some cases of congenital muscular dystrophy may arise from a fibre type disproportion at birth. However Case 8 presented with respiratory failure at 4 months of age, and the absence of severe neuromuscular problems in the early months of life makes the clinical diagnosis of congenital muscular dystrophy unlikely.

The clinical differential diagnosis of CFTD includes a number of other conditions. The picture initially may suggest a severe form of spinal muscular atrophy. In view of the very different prognosis in these two conditions it is clearly important to distinguish them, even to the extent of performing a muscle biopsy.

The combination of foot deformities, congenital dislocation of the hip, and flexion contractures often leads to a diagnosis of arthrogryposis multiplex congenita. This condition is a clinical definition of what is probably a heterogeneous group of disorders (Wynne-Davies and Lloyd-Roberts, 1976), some of which are myelopathic in origin presenting as 'wooden dolls' (Brandt, 1947), and others myopathic with weakness, hypotonia, and flexion contractures (Adams, 1975). Muscle biopsy may be the only way of distinguishing CFTD from this latter group.

Although none of our patients had contractures at birth, several soon developed them. These contractures present a different clinical problem from the rigid contractures of arthrogryposis multiplex congenita, and we feel the combination of weakness, hypotonia, and posture are significant aetiological factors.

Only one child (Case 7) had bilateral congenital talipes equinovarus at birth, which contrasts with its more usual incidence in arthrogryposis multiplex congenita (Lloyd-Roberts and Lettin, 1970). Calcaneo-valgus deformity of the feet was seen in 3 patients, requiring elongation of the extensor tendons and dorsal capsulotomy of the ankle joint in one.

Finally in the clinical differential diagnosis, is the syndrome of multiple congenital dislocations associated with characteristic facial abnormality (Larsen *et al.*, 1950). This diagnosis was initially given to 2 of our patients before muscle biopsy and it is important to distinguish this condition from CFTD as the management of the congenital dislocated hip is different. In Larsen's syndrome reduction of the dislocated hips has proved to be unrewarding (G. Lloyd-Roberts, personal communication), whereas in CFTD it is worth while.

Approximately one-third of our cases had dislocated hips and this is similar to the incidence reported by Brooke (1973). In his series good results were obtained with conservative treatment. This has not been our experience. All hips which were dislocated have required open reduction.

One of our patients was immobilised for a prolonged period after fracturing her tibia and a consecutive operation on her tendo achillis. She became noticeably weaker after this. Briefer periods of immobilisation for operative procedure in the other patients has not been followed by any physical deterioration.

Extensive investigations of the gastrointestinal tract in one pateint did not show any abnormality. As yet there is no explanation for the observation that many children with CFTD have heights and weights below the 3rd centile.

The question of inheritance of CFTD is an interesting one. None of our cases had an affected parent or sibling, but Case 6 of the series of Brooke and Engel (1969) had an elder brother with similar clinical features, and the father of these 2 boys was also said to have been weak as a child but to have outgrown the condition. Neither the brother nor the father of the index patient was biopsied and we feel from the information presented that the father did not have the same condition as his 2 sons. Fardeau *et al.* (1975) also reported a father and 2 siblings. However the father had at no time had any muscle weakness and his biopsy contained nemaline bodies and these features lead is to suspect that he too did not have the same condition as his children. Kinoshita *et al.* (1975) reported a boy and his mother who both had type 1 fibre atrophy and also nemaline bodies present on muscle biopsy. Although the authors felt that these patients had CFTD, we think their condition should be more properly called nemaline myopathy. It seems likely therefore that CFTD is inherited as a recessive trait.

From our experience of these 9 cases we agree with the general opinion that CFTD is a histological diagnosis which is usually associated with a clinical presentation having a favourable prognosis. However the progressively deteriorating clinical and histochemical features of our Case 8 lead us to agree with

Spiro *et al.* (1977) that a benign outlook is not invariable.

We thank Dr D. G. F. Harriman for allowing us to review the sections of the first biopsy from Case 9, and Drs E. M. Brett, R. Dinwiddie, D. N. Grant, J. Wilson, and Mr G. C. Lloyd-Roberts for permission to study their patients.

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Echocardiographic findings of large patent ductus arteriosus in the very low birthweight infant before and after treatment with indomethacin

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SUMMARY 17 very low birthweight infants (mean birthweight 850 g) with large patent ductus arteriosus (PDA) were studied by echocardiography before and after treatment with indomethacin. Before treatment left heart dimensions were increased suggesting large left-to-right shunt. Echographic measurements of augmented left ventricular (LV) contraction could be attributed to increase in preload, and reduction in afterload in PDA. After indomethacin, in infants showing clinical response, left heart dimensions returned rapidly to normal and LV contraction became normal or reduced. Two infants had reduced LV contraction with persistent pulmonary oedema suggesting LV failure. In contrast, infants showing no clinical response to the drug also had no significant changes in echographic measurements. Right ventricular systolic time intervals (RPEP/RVET) did not alter after indomethacin treatment in either group, suggesting that the drug does not increase pulmonary vascular resistance.

Echocardiographic assessment of left-to-right ductus shunt by measuring the left heart dimensions has been a major advance in the management of infants with patent ductus arteriosus (PDA). From left atrial to aorta ratio (LA/Ao) (Silverman *et al.*, 1974), left atrial dimension (LAD), and left ventricular end-diastolic dimension (LVEDD) (Baylen *et al.*, 1975) the size of shunt can be estimated. The echocardiogram can also be used to assess left ventricular performance (Sahn *et al.*, 1974) and pulmonary vascular resistance in the newborn (Hirschfeld *et al.*, 1975a; Riggs *et al.*, 1977). Measurements of left ventricular function in infants with PDA before and after ductus ligation have already been reported (Baylen *et al.*, 1977), but no data are available on the effects of indomethacin on left ventricular function and pulmonary vascular resistance in infants with large PDA. The purpose of this paper is to present our echocardiographic findings in 17 very low birthweight infants with large PDA who were given indomethacin.

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Patients and methods

17 infants of mean gestational age 27·2 weeks and mean birthweight 850 g were given indomethacin in a total dose of 0·2 to 0·6 mg/kg for large PDA. The diagnosis of PDA and the method of administration of the drug have been described elsewhere (Halliday *et al.*, 1979). The mean total dose of indomethacin was 0·38 mg/kg and the median age at treatment was 6 days (range 4–66). Four infants had severe respiratory distress (requiring $F_{IO_2} > 0 \cdot 60$ and assisted ventilation after 24 hours of age). 15 infants were treated with mechanical ventilation, one with mask CPAP, and one did not require ventilatory support when the drug was given. Six infants had been treated with digoxin and 5 with frusemide before being given indomethacin. There were 13 girls and 4 boys.

Echocardiograms were recorded using an Ekoline 20 ultrasonoscope (Smith-Kline Instruments) with a 5 MHz focused transducer. Studies were performed serially before giving indomethacin and within 3 days afterwards (mean 1·3). LAD and LVEDD were measured using methods previously described (Feigenbaum, 1972). LA/Ao was measured using the method of Silverman *et al.* (1974) (coefficient of variation ± 7·0%). Percentage shortening of the internal diameter (SID) of the left ventricle was calculated from the formula (Baylen *et al.*, 1977):

$$\%\,SID = (LVEDD - LVESD)/LVEDD \times 100$$

where LVESD = left ventricular end systolic dimension (Fig. 1). The systolic time intervals of both ventricles, the pre-ejection period (PEP), and ventricular ejection time (VET) were measured as previously described (Hirschfeld *et al.*, 1975b; Halliday *et al.*, 1977) (Fig. 2). Many of these tiny infants were being mechanically ventilated at the time of study and this may alter these measurements. For this reason at least 10 consecutive ventricular systoles were examined to give the mean systolic time intervals (coefficient of variation ± 4·8%).

Values before and after indomethacin were compared by the paired Student's *t* test.

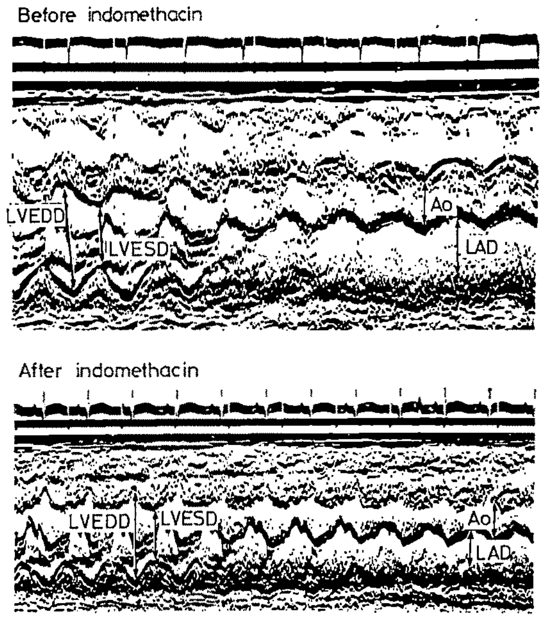

Fig. 1 *Echocardiograms of left ventricle with sweep to aorta and left atrium before and after indomethacin treatment for large PDA in a 750-g infant. The echocardiograms are not recorded on the same scale. Fig. 1a (before indomethacin) shows left ventricular end-distolic dimension (LVEDD) = 1·7 cm, left ventricular end-systolic dimension (LVESD) = 0·9 cm, percentage shortening of internal dimension of LV (% SID) = 47%, left atrial dimension (LAD) = 0·9 cm, and left atrial to aorta ratio (LA/Ao) = 1·6:1. After indomethacin (Fig. 1b) the measurements become LVEDD = 1·35 cm, LVESD = 0·8 cm, % SID = 41%, LAD = 0·7 cm, and LA/Ao = 1·2:1.*

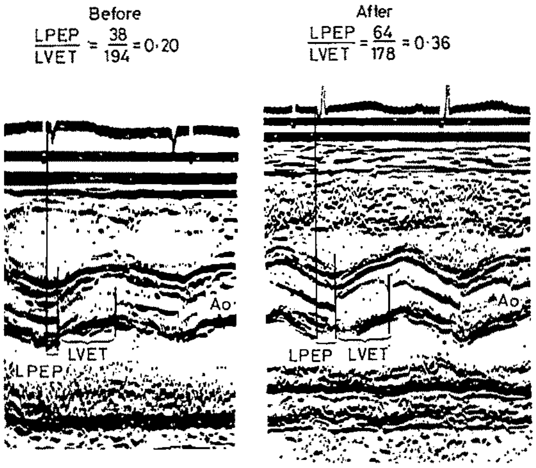

Fig. 2 *Echocardiograms of aortic valve at paper speeds of 100 mm/s before and after treatment with indomethacin in a 750-g infant. Before treatment left ventricular pre-ejection period (LPEP) = 38 ms, left ventricular ejection time (LVET) = 194 ms, and LPEP/LVET = 0·20. After treatment LPEP = 64 ms, LVET = 178 ms, and LPEP/LVET = 0·36.*

Results

After treatment with indomethacin, 13 of 17 infants showed good clinical response with reduced intensity of the murmur, decreased pulses and praecordial activity, and less need for ventilatory support (group 1). Within 3 days the PDA had closed in these infants. The remaining 4 infants showed little or no clinical response to indomethacin (group 2). These two groups of infants were of similar gestational ages, birthweights, sexes, and age at treatment. Incidence of severe respiratory distress, and pretreatment with digoxin or frusemide was also similar (Table 1).

Echocardiographic findings before treatment were similar in both groups (Table 2).

Table 1 *Comparison of clinical characteristics of infants with and without clinical response to indomethacin (mean ± 1 SD)*

	Group 1 (n=13) Responders	*Group 2 (n=4) Nonresponders*	*P*
Gestational age (weeks)	27·3±1·3	27·0±1·6	NS
Birthweight (g)	845±180	875±195	NS
Sex (male/female)	4/9	0/4	NS
Severe respiratory distress	3 (23%)	1 (25%)	NS
Prior digoxin therapy	4 (36%)	1 (25%)	NS
Median age at treatment (days)	6 (4–66)	7 (4–39)	NS
Total dose of indomethacin (mg/kg)	0·40±0·16	0·32±0·16	NS

Table 2 *Comparison of echocardiographic and blood pressure findings before and after treatment with indomethacin in groups 1 and 2*

	Group 1 (responders) (n=13)			*Group 2 (nonresponders) (n=4)*		
	Before	*After*	*P*	*Before*	*After*	*P*
HR (beats/min)	149	142	NS	149	148	NS
LAD (cm)	1·05	0·72	<0·001	0·90	0·90	NS
LA/Ao	1·69	1·16	<0·001	1·49	1·43	NS
LVEDD (cm)	1·45	1·21	<0·01	1·15	1·08	NS
% SID (%)	40·4	34·8	<0·01	40·5	39·5	NS
LPEP (ms)	42	56	<0·001	45	47	NS
LVET (ms)	181	165	<0·02	176	174	NS
LPEP/LVET	0·23	0·35	<0·001	0·25	0·27	NS
RPEP/RVET	0·33	0·31	NS	0·35	0·31	NS
SBP (mmHg)	51	62	<0·01	52	51	NS
DBP (mmHg)	24	30	<0·01	27	29	NS

HR = Heart rate; LAD = left atrial dimension; LA/Ao = left atrial to aorta ratio; LVEDD = left ventricular end diastolic dimension; % SID = percentage shortening of the internal dimension of LV; LPEP = left ventricular pre-ejection period; LVET = LV ejection time; RPEP = right ventricular pre-ejection period; RVET = RV ejection time; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Left heart dimensions (LAD, LA/Ao, and LVEDD). These echographic measurements of left heart size were increased before treatment in both groups when compared with normal values of Baylen *et al.* (1975, 1977) and Silverman *et al.* (1974) (Figs 1 and 3). Our normal LA/Ao values are somewhat higher than those of Silverman *et al.* (1974) 1·1 ± 0·1 (H. L. Halliday and J. Keroes, 1977, unpublished observations). The measurements in responding infants (group 1) tended to be higher than those in nonresponding ones (group 2) (Table 2) but the differences were not statistically significant. After indomethacin treatment, group 1 infants showed decrease in left heart dimensions to the normal range (Fig. 1b), often within 24 hours and, in 2 infants, by 4 hours after administration. Fig. 4 shows measurements from a typical infant.

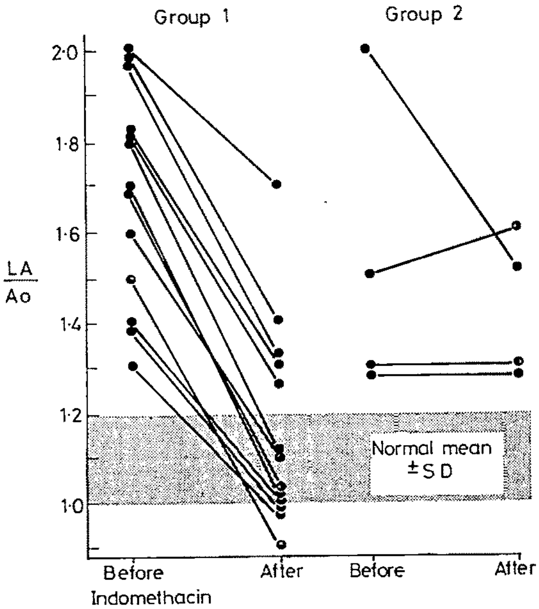

Fig. 3 *Comparison of changes in LA/Ao ratio after treatment with indomethacin in groups 1 and 2. Shaded area represents normal mean ± 1 SD (H. L. Halliday and J. Keroes, 1977, unpublished observations).*

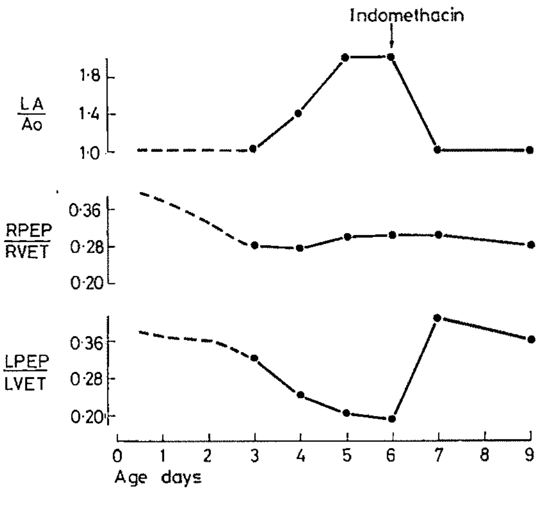

Fig. 4 *Measurement from serial echocardiograms of a 750-g infant who developed a large PDA. Dashed lines show previously reported results (Silverman et al., 1974; Halliday et al., 1978). As clinical evidence of PDA appears about the fourth day of life, LA/Ao ratio increases and LPEP/LVET ratio decreases while RPEP/RVET ratio is unchanged. Indomethacin was given on day 6 and LA/Ao and LPEP/LVET rapidly returned to normal while RPEP/RVET did not change.*

Percentage shortening of internal dimension of LV (% SID). Levels before treatment were about 40% (normal = 33·5%). After treatment group 1 infants had a decrease in % SID to 34·8% ($P<0·01$), but group 2 infants showed no such change (Table 2 and Fig. 5).

Systolic time intervals. In both groups mean LPEP/LVET was less than 0·26 (Figs 2 and 6) and normal for preterm infants without PDA is 0·32 (Halliday *et al.*, 1978). The ratio was decreased as a result of reduced LPEP and increased LVET (Table 2). After treatment values returned to normal in group 1 (Figs 2 and 6). Mean RPEP/RVET ratios were normal in both groups and were unaffected by indomethacin.

Blood pressure and heart rate (Table 2). Heart rate did not alter in either group but blood pressure in responding infants increased significantly from mean 51/24 to 62/30 mmHg.

Correlations. LPEP/LVET was negatively correlated with LA/Ao by the following formula: $\text{LPEP/LVET} = -0·14\,(\text{LA/Ao}) + 0·48$ ($r = -0·67$) and positively with diastolic blood pressure—$\text{LPEP/LVET} = 0·004\,(\text{DBP}) + 0·17$ ($r = 0·45$).

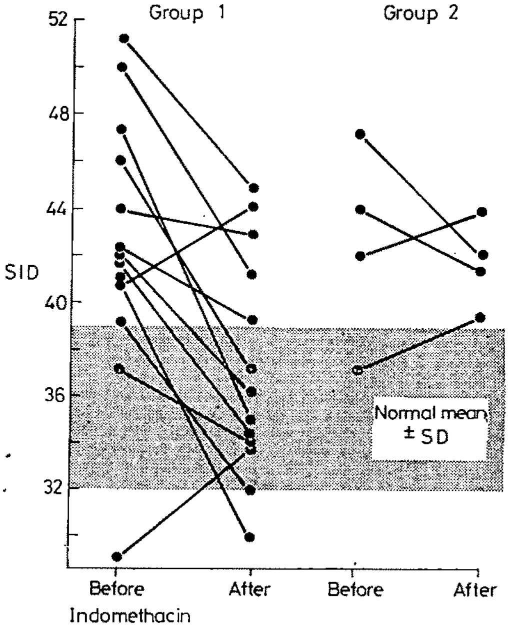

Fig. 5 *Comparison of % SID changes before and after treatment with indomethacin in groups 1 and 2. Shaded area represents normal mean ± 1 SD (Baylen et al., 1975, 1977).*

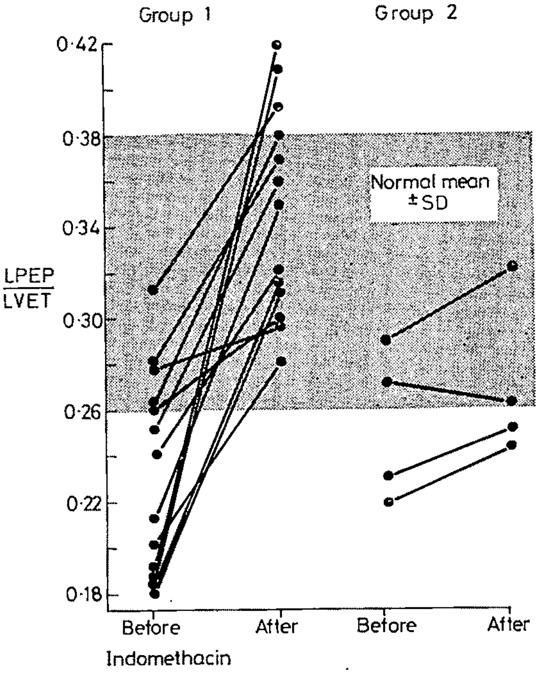

Fig. 6 *Comparison of changes in echocardiographic ratio LPEP/LVET in groups 1 and 2 after indomethacin treatment. Shaded area represents normal mean ± 1 SD (Halliday et al., 1978). Note the 2 infants in group 1 in whom LPEP/LVET was over 0·40 after treatment.*

Discussion

In the infant with large PDA, torrential left-to-right shunt will result in left ventricular and left atrial dilatation (Silverman *et al.*, 1974; Baylen *et al.*, 1975). Left atrial and left ventricular end-diastolic dimensions, and left atrial to aorta ratio have been shown to increase in left-to-right shunts including large PDA. After ductus ligation these dimensions rapidly revert to normal (Silverman *et al.*, 1974; Baylen *et al.*, 1975). There have been relatively few echocardiographic studies of left ventricular function in large PDA (Kaye *et al.*, 1975; Sahn *et al.*, 1976; Baylen *et al.*, 1977). Because of the reduced afterload, shortening of left ventricle (% SID) will increase and may spuriously suggest improved left ventricular contractility in PDA (Quinones *et al.*, 1975). Similarly, the ratio LPEP/LVET, which has been used as a measure of LV contractility (Weissler *et al.*, 1969; Halliday *et al.*, 1977), will be influenced by reduction in afterload in PDA.

Our infants with large PDA had increased left

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heart dimensions and presumably raised LV preload. In addition, increased % SID, and decreased LPEP/LVET could be reflections of the decreased afterload. After indomethacin administration left heart dimensions decreased rapidly and the changes were similar to those observed after ductus ligation. In indomethacin-treated infants whose murmurs remained, no significant reduction in left heart dimensions occurred. Although only 4 such infants were studied, 3 needed subsequent ductus ligation for continued failure. These infants probably attained similar blood levels as responding infants because they developed reduced urinary excretion of similar severity (Halliday *et al.*, 1979). Responding infants also demonstrated reduction in % SID, and increase in LPEP/LVET. We attribute these changes to increase in LV afterload and decrease in preload to normal levels after closure of the ductus. This is consistent with the relationship found between LPEP/LVET and diastolic blood pressure (afterload) and LA/Ao ratio (preload). It is possible however, that indomethacin had a direct myocardial depressive effect. The drug has been shown to raise coronary vascular resistance in the isolated animal heart without changing performance (Schror *et al.*, 1976), and a recent report of infant death from myocardial infarction and pneumonia after treatment with indomethacin has been published (Merritt *et al.*, 1978). Nevertheless, we feel that the signs of decreased LV contractility after indomethacin were due to the effect of ductus closure rather than to myocardial depression as they did not occur in infants whose ductus remained open. Furthermore the changes were similar to those after ductus ligation (Park *et al.*, 1973; Baylen *et al.*, 1975).

In 2 infants the echographic signs of decreased LV contractility were exaggerated with % SID below 32 and LPEP/LVET over 0·40 after treatment. These infants had persistent signs of pulmonary oedema, despite clinical closure of the ductus. This finding is in keeping with previous reports of depressed LV function after ductus ligation (Park *et al.*, 1973; Baylen *et al.*, 1975). We feel that LV failure resulted from rapid ductus closure with sudden increase in afterload to normal levels which stressed the already dilated and compromised LV.

Right ventricular systolic time intervals (RPEP/RVET) have been shown to correlate with pulmonary vascular resistance in infants and children (Hirschfeld *et al.*, 1975a). Despite a recent study showing increased pulmonary vascular resistance after administration of indomethacin to premature goats (Tyler *et al.*, 1975) we found no echocardiographic evidence to support this finding in our very low birthweight infants.

In summary, very low birthweight infants with large PDA have echocardiographic evidence of increased left heart dimensions and augmented LV contraction as a result of increased preload and reduced afterload. After ductus closure with indomethacin left heart dimensions rapidly return to normal (in 2 infants within 4 hours of treatment). There was no evidence of increased pulmonary vascular resistance after treatment but 2 infants showed signs of decreased LV contractility and had persistent pulmonary oedema possibly due to LV failure. This we attribute to the effects of rapid ductus closure with sudden increase in afterload rather than to direct myocardial depression by indomethacin.

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A prospective study of 18 infants of chronic HBsAg mothers

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SUMMARY 28 of 1002 pregnant Sicilian women (2·8%) were asymptomatic HBsAg chronic carriers. 18 children of these women were followed and at least 15 of them showed evidence of transplacental infection with HBsAg, resulting either from the presence of the antigen in cord blood, or from the development of the corresponding antibody in the serum within the first 2 months of life. Despite this, only 2 or 3 of the infants developed chronic antigenaemia from age 2–4 months. Only the infants whose mothers were HBeAb-negative, and who themselves remained HBsAb-negative during the first months of life, became HBsAg carriers. On the basis of these results, a strategy is suggested for selecting infants from areas with a high prevalence of HBsAg carriers so that they can be given passive immunisation with hyperimmune globulin.

The application of new techniques for demonstrating hepatitis B surface antigen (HBsAg) to the study of maternofetal transmission of hepatitis B (so-called vertical transmission) has raised more questions than it has resolved. Unresolved problems include the prevalence of cord blood antigenaemia in children of chronic carrier mothers, the successive development, duration, and clinical implications of the antigenaemia in these children, and the possibility of its prevention.

In order to obtain information on these topics, we identified a group of pregnant women who were asymptomatic chronic HBsAg carriers, and followed their children for several months after birth, with clinical and laboratory examinations.

Our study indicated that HBsAg-positive mothers usually transmit the antigen to their babies, but also that only a few of these infants develop persistent antigenaemia with or without signs of hepatitis. On the basis of these findings we suggest a possible strategy for the prevention of persistent HBs antigenaemia in children of carrier mothers.

Materials and methods

1002 unselected pregnant women admitted to this maternity hospital, where over 6000 deliveries a year take place, were screened for HBsAg by the reverse haemagglutination method (Hepanosticon, Organon). All the positive sera were retested by radioimmunoassay (AUSRIA II, Abbott Laboratories) and confirmed to be positive, and determinations of bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT) were made. A second radioimmunoassay for HBsAg was made after 3–6 months in order to confirm the chronic carrier state.

The HBsAg-positive women were also tested for HBcAb, by radioimmunoassay (CORAB, Abbott Laboratories), and for HBeAg and HBeAb by immunodiffusion techniques, using e antigen and antibody kindly supplied by Dr Linsen (Copenhagen).

The babies of the HBsAg-positive mothers were examined clinically at monthly intervals, and their sera tested for HBsAg (AUSRIA II, Abbott Laboratories), HBsAb (AUSAB, Abbott Laboratories), bilirubin, AST, and ALT. The babies were all formula fed. When available, their fathers were also studied.

Results

28 of the 1002 women (2·8%) were asymptomatic

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chronic carriers of HBsAg. None had a history of clinical hepatitis, jaundice, or liver enlargement; serum transaminases and bilirubin levels were normal. The 28 women were informed of their condition and advised that their babies should be periodically examined. Eventually, 18 of the 28 children of chronic carrier mothers were kept under observation for 3–14 months. The results were as follows (Figure). (1) Five of the 9 cord bloods examined were HBsAg-positive. One child with HBsAg-positive cord blood was born by caesarean section (Case 4). But the positivity for HBsAg in the cord blood was transient as all the sera examined 2–3 days later were consistently HBsAg-negative. (2) In 10 (56%) of the 18 children a weak but definite positivity for HBsAb was found for the first time in the sera obtained at 1–2 months of age. None of these children had previously been HBsAg-positive, apart from 3 transient positives in cord blood (Cases 4, 9, and 14, Figure). Even the HBsAb-positivity was generally transient; only in Case 9 was it still present in the last examination at 7 months. (3) Four of the 18 children became HBsAg-positive between 2 and 4½ months. This incubation period is in agreement with previous work, suggesting that infection with HBsAg usually takes place during the immediate perinatal period. Details of these 4 cases were as follows.

Case 1. This asymptomatic infant, whose cord blood was HBsAg-positive, showed HBsAg positivity with slightly increased AST and ALT only on one other occasion at 4½ months. This positivity was transient and was followed by appearance of HBsAb at age 10 months.

Case 3. HBsAg was found for the first time at 4 months, accompanied by markedly increased AST and ALT and by slight liver enlargement without jaundice or other clinical symptoms. The raised transaminase levels persisted during the observation period (up to 14 months). A liver biopsy at 7 months showed histological features of chronic hepatitis (interstitial fibrosis with mononuclear infiltrates, with some disorganisation of the lobular architecture).

Case 11. At 2 and at 3 months this asymptomatic child, who had been previously HBsAg-negative, showed HBsAg positivity and moderately increased transaminase levels.

Case 18. HBsAg was present from age 2 months up to the last examination at 6 months. Serum transaminases were normal, and there were no clinical symptoms.

A negative correlation was found between early

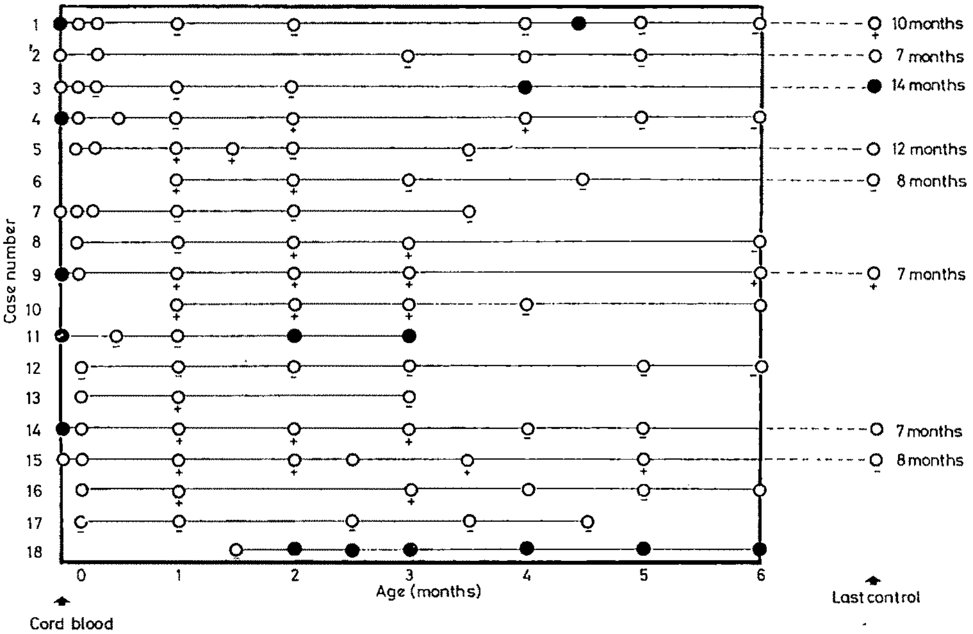

Figure *HBs antigen and the corresponding antibody in 18 children of chronic HBsAg carrier mothers. + = positivity, — = negativity for HBsAb ● = positivity, O = negativity for HBsAg.*

Table 1 *Hepatitis-associated antigens and antibodies in 18 infants of HBsAg carrier mothers and in their parents*

Case	*Father*		*Mother*				*Cord serum*	*Infant*	
	HBsAg	*HBsAb*	*HBsAg*	*HBcAb*	*HBeAg*	*HBeAb*	*HBsAg*	*HBsAb*	*HBsAg*
1	−	−	+	+	−	+	+	−	+
2	−	−	+	+	−	+	−	−	−
3	−	−	+	+	−	−	−	−	+
4	ND	ND	+	+	ND	ND	+	+	−
5	−	+	+	+	−	−	ND	+	−
6	−	+	+	+	−	−	ND	+	−
7	−	±	+	+	−	+	−	−	−
8	−	+	+	+	−	+	ND	+	−
9	−	−	+	+	−	+	+	+	−
10	−	+	+	+	−	+	ND	+	−
11	−	−	+	+	−	−	+	−	+
12	−	±	+	+	−	+	ND	−	−
13	−	−	+	+	−	+	ND	+	−
14	+	−	+	+	−	+	+	+	−
15	−	+	+	+	−	+	−	+	−
16	−	−	+	+	−	+	ND	+	−
17	−	+	+	+	−	−	ND	−	−
18	−	+	+	+	ND	ND	ND	−	+

+ = Positive, − = negative, ND = not done.

positivity for HBsAb and the development of HBsAg positivity: all 10 HBsAb-positive children remained HBsAg-negative, while 4 of the 8 HBsAb-negative children became HBsAg-positive. This difference is significant at the 0·01 level by the χ^2 method.

(4) 16 of the 18 mothers were studied for HBeAg and HBeAb (Table 1). All were HBeAg-negative, while 11 were HBeAb-positive. Persistent HBsAg positivity developed, at 3 and 4 months of age, in 2 of the 5 children born to HBeAb-negative mothers, and in none of the 11 children born to HBeAb-positive mothers. Only one of these developed HBsAg positivity at age 4½ months; this rapidly disappeared and was followed by the development of HBsAb (Case 1, Figure).

This difference is significant at the 0·025 level.

(5) All the 18 HBsAg-positive mothers, including those whose children became HBsAg positive, were tested for HBcAb and found positive.

(6) Only one of the 17 fathers studied was a HBsAg carrier like his wife. The child born to this couple was positive for HBsAb at 2 and 4 months, and at 6 months he was still HBsAg-negative.

Discussion

While there may well be pronounced ethnic differences in the frequency with which HBsAg is transmitted by carrier mothers to their babies, recent studies using sensitive detection methods have shown this frequency to be quite high in all countries (Table 2).

Table 2 *Newborn infants of chronic carrier mothers who were followed up*

Country	*Authors*	*Year*	*Carrier mothers (%)*	*Infants*			*Method**	*Follow-up (months)*
				Studied	*Positive*	*Persistently positive*		
Denmark	Skinhøj *et al.*	1972	0·12	36	0	0	GEP	3–12
		1976		30	1	1	RIA	48–60
Pakistan	Aziz *et al.*	1973	1·52	18	1	1	CEP	>70
USA	Schweitzer *et al.*	1973	0·49	21	1	1	CEP	≥3
	Gerety and Schweitzer	1977		14	6	5	RIA	>6
Thailand	Punyagupta *et al.*	1973	9·39	14	0	0	ID	6
Greece	Papaevangelou *et al.*	1974	3·27	15	1	1	RIA	6
Taiwan	Anderson *et al.*	1975	7·50	43	27	≥20	CF-RIA	1–18
	Stevens *et al.*	1975	15·20	158	63	35/38	RIA	1–18
Japan	Okada *et al.*	1975	2·32	11	8	8	IAHA	8–26
		1976	2·50	23		12	IAHA	≥12
Italy	Chircu *et al.*	1975	2·25	6	1	0	RIA	2–5
France	Dupuy *et al.*	1978	0·63	12	8	1	RIA	6–18
Italy	Present series		2·80	18	4	2 or 3	RIA	3–14

*GEP = Gel electrophoresis, RIA = radioimmunoassay, CEP = counter electrophoresis, ID = immunodiffusion, CF = complement fixation, IAHA = immunoadherence haemagglutination.

Direct evidence of maternofetal transmission is given by the HBsAg positivity of cord blood at birth. In this respect, in agreement with other recent studies (Schweitzer *et al.*, 1973; Boxall and Davies, 1974; Papaevangelou *et al.*, 1974; Chircu *et al.*, 1975), we found a high percentage of positivity (5 of the 9 cord bloods examined). But the present study gives additional, indirect evidence of maternofetal transmission of HBsAg even in those children in whom HBsAg has not been directly demonstrated. In fact, many infants of our series, previously repeatedly HBsAg-negative by radioimmunoassay, developed antibodies against this antigen within the first 2 months of life. A postnatal infection of these infants is extremely unlikely, because of this high frequency of an early appearance of HBsAb. By adding to the subjects with HBsAg-positive cord blood those who developed HBsAb early in life, we have direct or indirect evidence of fetal infection with HBsAg in 13 of the 18 infants. We could add to these another 2 infants (Cases 3 and 18, Figure) in whom HBsAg appeared at 4½ and at 2 months, even if postnatal infection cannot be ruled out for these subjects, particularly for Case 3.

Despite this high transmission rate, only a few children (2 or 3 out of 18 in our series) developed persistent HBs antigenaemia. It is probable therefore that in most subjects there are some protective factors.

Okada *et al.* (1976), in a series of mother-child pairs recently studied in Japan, found that the children of HBeAg-positive mothers all became HBsAg-positive, while the children of mothers with HBeAb remained HBsAg-negative. More recent studies (Gerety and Schweitzer, 1977; Dupuy *et al.*, 1978) have raised some doubts about the infecting role of maternal HBeAg, while the protective role of maternal HBeAb has been fully confirmed: in these series, HBs-antigenaemia developed in only one child of a HBeAb-positive mother, but was transient and was rapidly followed by the appearance of HBsAb. Our series comprises one other child with an identical pattern, and clearly confirms that maternal HBeAb always prevents the development of chronic HBs antigenaemia in these children. As (as in the study of Papaevangelou *et al.*, 1974) all the 18 mothers of our study were HBcAb positive, the results do not suggest that maternal HBcAb prevents HBsAg infection of the conceptuses.

By contrast, a significant protective role is played by the HBsAb produced by the infant from the first weeks of life. The 3 infants who became persistently HBsAg-positive were all born to HBeAb-negative mothers, and none of them had been HBsAb-positive in the first 2 months of life. On the other hand, none of the children whose mothers were HBeAb-positive, or who themselves had been HBsAb-positive, became a HBsAg carrier.

On the basis of these results, a strategy is indicated to prevent persistent antigenaemia in children of HBsAg carrier mothers in areas with a high prevalence of HBsAg carriers. (1) Each pregnant woman should be tested for HBsAg. (2) Each HBsAg-positive woman should be tested for HBeAb. (3) Each child of an HBsAg+, HBeAb− mother is at risk and administration of HBsAg hyperimmune gammaglobulin should be considered, or (4) each child of an HBsAg+, HBeAb− mother who remains HBsAb− during the first 6 weeks of life is at risk and administration of HBsAg hyperimmune gammaglobulin should be considered.

Kohler *et al.* (1974) and Dosik and Jhaveri (1978) have suggested that a chronic HBsAg carrier state might be prevented by the administration of hyperimmune HBsAg globulins in the immediate postnatal period. A control trial of such treatment in infants selected in the above fashion could provide useful data.

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Virus infections in children with acute lymphoblastic leukaemia

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SUMMARY The pattern of virus isolation and illness was studied in 64 children with acute lymphoblastic leukaemia (ALL) during periods of apparent infection and when the children were well. The virus isolation rate of 2·2 viruses per child a year is similar to that previously found in normal children. In only 32% of children with symptoms were viruses found and 14·5% had viruses isolated when asymptomatic. The children with ALL appear to be more vulnerable to multiple virus infections and to excrete the virus for longer periods. This may be due to failure of production of both local and systemic antibodies. The failure in the past to recognise the true importance of virus infections in ALL may have been due to inadequate diagnostic techniques.

Infections are playing an increasingly important role in the death of children with acute lymphoblastic leukaemia (ALL) and viruses are emerging as important pathogens (Craft *et al.*, 1977). While it is recognised that varicella zoster and measles may be particularly severe in the immunosuppressed host (Feldman and Cox, 1976), it has been suggested that the common upper respiratory virus infections are neither more frequent nor more severe in children with ALL (Levine *et al.*, 1974). However, there has been little systematic study of virus infections in this disease. In the present investigation viruses were studied in children with ALL, both when an infection was suspected and when the children were well. The results are presented in the light of locally acquired experience of virus infections in normal children.

Patients and methods

64 children with ALL, 34 boys and 30 girls, were followed for at least 2 months, some for as long as 33 months. Their ages at diagnosis ranged from 1½ to 14 years. All were being treated with conventional combination chemotherapy and prophylactic cranial irradiation and most were on a modified ALGB 6801 regimen (Reid *et al.*, 1977). During the initial phase of the investigation children were studied only when they were suspected of having an infection. 31 such children were followed for a total of 468 patient months. The remaining 33 children were investigated when they were infected and also routinely at monthly intervals. They were followed for a total of 397 patient months. When an infection was suspected a specimen of nasopharyngeal secretion was investigated by the fluorescent antibody technique (FAT) (Gardner and McQuillin, 1974). Nose and throat swabs were obtained at the same time and cultured for viruses. The routine monthly investigations consisted only of nose and throat swabs. Varicella zoster was identified by fluorescent antibody staining of scrapings of skin lesions. All isolations by the FAT were confirmed by subsequent culture. No attempt was made to isolate viruses from faeces or urine. Whenever possible further specimens were taken after the initial diagnosis of a virus infection until the child ceased to excrete the virus. Specimens of blood both in the acute and convalescent phases were taken from many of the patients

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and the titre of complement fixing antibody to the isolated virus was determined.

The clinical features of the illnesses caused by viruses were divided according to whether or not the child was asymptomatic, had a mild to moderate illness which was not more severe than would be expected in a normal child and for which admission to hospital was not required, symptoms which were much more severe than usual requiring admission to hospital and often life threatening, and those which were associated with the death of the child although not necessarily the direct cause of death.

Controls

Control information was obtained from normal children admitted to local hospitals in recent years because of a virus infection and investigated using identical techniques in the same laboratory as in this study. A group of 796 normal children was studied to define the rate of multiple virus isolation in a single infective episode.

The length of time for which influenza A, respiratory syncytial virus (RSV), or measles was excreted by normal children was obtained by examination of follow-up specimens taken after the diagnosis of the infection. Generally no further specimen was taken after the child was clinically well or discharged from hospital.

The pattern of rise of complement fixing antibodies to influenza A and measles in normal children was obtained from the same group of children, but for RSV the control data were confined to those older than one year. However, the effect of local nasopharyngeal blocking antibodies on the rate of isolation of RSV from normal children (Gardner and McQuillin, 1978) was studied in children of all ages.

Results

During the initial phase of the investigations 31 patients were followed for a total of 468 patient months and 46 viruses were obtained, with an isolation rate of 1·2 viruses per child a year. The remaining 33 children, who were also swabbed routinely at monthly intervals, were followed for 397 patient months and 73 viruses were isolated, an isolation rate of 2·2 viruses per child a year. 119 viruses were isolated from 50 of the 64 children during 99 infective episodes. 14 were at no time infected with a virus that could be detected by these techniques. The viruses isolated and the severity of illnesses are shown in Table 1. 15 children had 21 severe illnesses associated with virus infections and clinical details of these are shown in Table 2. The 33 asymptomatic virus isolations were all made during the second phase of the study. In many of the children who had symptoms suggesting a virus infection it was not possible to isolate one, and the relationship between the presence of symptoms and the isolation of virus is shown in Table 3.

18 children had more than one virus isolated during the same illness, 15 had a dual infection once, 2 on two occasions, and 1 child had three viruses isolated simultaneously. Multiple virus isolations were therefore present in 20 (20%) of the 99 episodes of virus infection. There were 20 multiple virus isolations in the 796 normal children, a rate of 2·5%. This difference is significant ($\chi^2 = 66{\cdot}5$, $P<0{\cdot}001$).

The length of time of excretion of RSV, influenza A, and measles is shown in Fig. 1 and is compared with data from normal children.

The antibody titres to RSV, influenza A, and measles during the acute and convalescent phases of the illness are compared with those from a group of normal children in Fig. 2.

Table 1 *Viruses isolated according to the severity of illness*

Virus	*Asymptomatic*	*Mild to moderate illness— not admitted*	*Severe illness— admitted*	*Associated with death*	*Total*
H-strain rhinovirus	13	16	4	4	37
Herpes virus hominis	13	10	3		26
Cytomegalovirus	5	1	4	2	12
Respiratory syncytial virus	1	7	2		10
Influenza					
A		6	5		11
B		2			2
Parainfluenza					
3		1	1	1	3
4			1		1
Adenovirus	1	5			6
Measles			2	1	3
Echovirus		1	3		4
Varicella zoster		2			2
Mumps		1		1	2

Table 2 *Clinical details of children who had a severe illness and were admitted to hospital*

Case		*Main clinical details*	*Length of illness (days)*	*Virus isolated*
1	September 1976	Pneumonitis, prolonged fever*	21	Cytomegalovirus
	November 1976	Fever, cough, petechial rash	4	H-strain rhinovirus
	February 1977	Pneumonitis, fever	7	Influenza A
2	July 1976	Fever, rash, splenomegaly	14	Cytomegalovirus
	August 1976	URTI, hepatosplenomegaly	14	H-strain rhinovirus
3	February 1976	Pneumonitis, otitis media, fever*	60	Respiratory syncytial virus + H-strain rhinovirus
	February 1977	Pneumonitis, otitis media, fever*	60	Respiratory syncytial virus + H-strain rhinovirus
4	August 1976	Pneumonitis, oral ulceration, fever	28	Herpes virus hominis
	March 1977	Pneumonitis, otitis media, fever	11	Influenza A
5		Otitis media, fever, rash	28	Cytomegalovirus + H-strain rhinovirus
6		URTI, fever, otitis media, meningitis*	12	Influenza A (also *Listeria monocytogenes* meningitis)
7		Gastroenteritis, oral ulceration, haematemesis*	10	Herpes virus hominis (also *Escherichia coli* septicaemia)
8		Severe pneumonitis*	26	Measles
9		Pneumonitis, *no* rash	14	Measles
10		Fever, submandibular swelling	7	Herpes virus hominis + echovirus
11		Fever, URTI, diarrhoea, abdominal pain	42	Parainfluenza 4
12		URTI, fever	4	Echovirus
13		Pneumonitis, fever, headache*	10	Parainfluenza 3
14		URTI, fever, cough, cervical lymphadenopathy*	28	Influenza A
15		Pneumonia, anorexia, prolonged fever*	35	Echovirus and cytomegalovirus

URTI = Upper respiratory tract infection.
*Life threatening.

Table 3 *Relationship between the presence or absence of symptoms suggestive of a virus infection and the isolation of a virus*

Virus	*Symptoms suggestive of virus infection*	*No symptoms*
Isolated	86	33
Not isolated	185	183

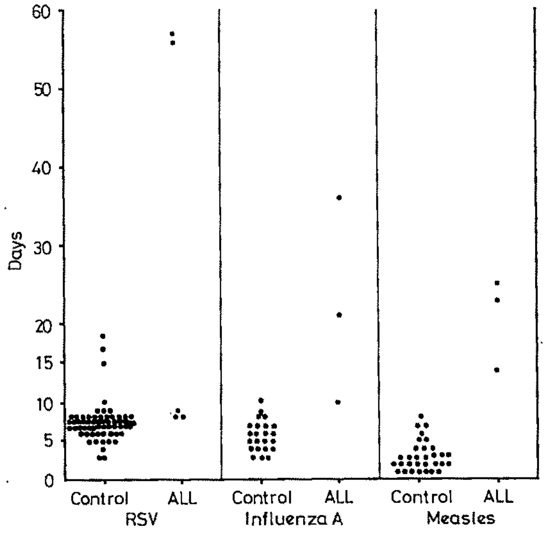

Fig. 1 *Length of excretion of RSV, influenza A, and measles virus in normal children and those with leukaemia.*

In the 5 children with RSV in whom follow-up specimens were taken it was possible to grow the virus as well as to demonstrate it by the FAT. However, of 150 normal children in whom RSV was demonstrated by the FAT in a follow-up specimen it was possible to grow the virus in only 59.

Discussion

There is very little information about the incidence of virus infections in normal children. Hurrell *et al.* (1971) studied two normal families at weekly intervals for a period of almost 2 years and found a virus isolation rate in the children of 2·3 viruses per child a year. The only other reported survey of virus infections in normal children is from the Seattle Virus Watch Programme but it is difficult to obtain a clear picture of virus isolation rates (Elveback *et al.*, 1966). The isolation rate of 2·2 viruses per child a year, during the second phase of the current study suggests that children with leukaemia may not be more susceptible than normal children to virus infections, although the isolation rate might have been higher had they been swabbed at weekly intervals. However, previous studies have included many children less than one-year old, whereas most of the children with ALL were considerably older than this. Young children are known to suffer from more respiratory infections than older ones (Miller *et al.*, 1974). Until more is known about viruses in the normal population it will not be

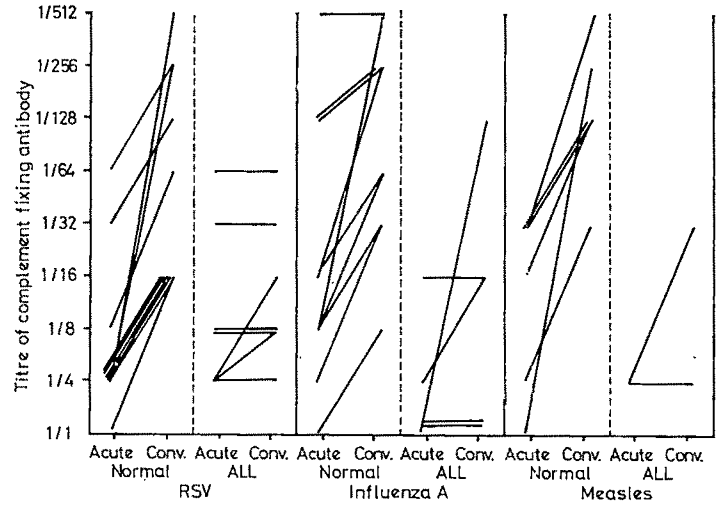

Fig. 2 *Titre of complement fixing antibody to RSV, influenza A, and measles virus in acute and convalescent phases of illness in normal children and those with leukaemia.*

possible to be certain about the susceptibility of children with ALL to these infections.

The isolation of viruses from asymptomatic children, and the failure to isolate a virus from an apparently infected child, are both well recognised phenomena (Elveback *et al.*, 1966). Elveback suggested that asymptomatic infections and excretion of virus were more common in younger than in older children. In the present study a virus was isolated from only 32% of the children with symptoms suggesting a virus infection. A virus was isolated from 15·3% of the routine swabs taken from asymptomatic children. It is difficult to compare these results with those obtained from the Seattle Virus Watch Programme because of differences in the techniques used for isolation and, in particular, because faecal specimens were also collected in the American study. However, it is clear that many children suffer upper respiratory tract infections whose cause, at present, remains unknown and also that apparently well children may be asymptomatic carriers of, in particular, cytomegalovirus, herpesvirus, and rhinovirus. Many of the illnesses were no more serious than similar virus infections in normal children. However, severe illnesses, which were often life threatening, were associated with 25 of the viruses isolated. Many of these children had prolonged illnesses necessitating interruption of their leukaemia treatment.

Nine viruses were associated with 6 deaths. The role of viruses in the death of children with ALL has been discussed in detail (Craft *et al.*, 1977).

Concurrent multiple virus isolations appear to be more common in children with ALL than in normal children, and this aspect of the study is being reported in detail elsewhere (Bruce *et al.*, 1979). The apparently increased susceptibility of children to multiple virus infections may be associated with prolonged excretion of viruses in many cases. Most normal children who have measles will have ceased to excrete virus by 3 or 4 days after the appearance of the rash and in a review from this laboratory none excreted for longer than 10 days (McQuillin *et al.*, 1976). Influenza viruses are not normally excreted for more than 9 days in children (Brocklebank *et al.*, 1972) and for only 3 or 4 days in adults (Knight *et al.*, 1970), whereas the children with ALL did so for much longer. Most children with RSV stop excreting the virus by 10 days. Although there is a great deal of information about RSV in normal children in Newcastle, much of this has been acquired from infants less than one-year old (Gardner, 1976). Older children rarely develop infections severe enough to require admission to hospital and they also excrete the virus for a shorter period of time than do infants (Hall *et al.*, 1976). All the children with ALL were older than one year, but some developed severe infections similar to those seen in normal infants. One child in the present study continued to excrete RSV for 56 and 57 days in two separate infective episodes one year apart. Rhinoviruses may be excreted for prolonged periods in normal children (Fox *et al.*, 1975) as was found in the children with ALL.

Changes in complex immunological mechanisms probably account for the increased severity and prolonged excretion of viruses in children with ALL. In the current study we have been able to look at two aspects of the immune system. In only 59 of 150 children in whom RSV was demonstrated by the FAT was it possible to grow the virus. Complex immunofluorescent staining techniques have shown that this is due to the production of local blocking antibodies which prevent replication of the virus but do not prevent its demonstration by the FAT (McQuillin *et al.*, 1970; Gardner and McQuillin, 1978). In the 5 children with leukaemia and RSV infection, follow-up specimens were all positive by both the FAT and viral culture and it was not possible to detect any local blocking antibodies. This failure of production of antibody to RSV is also shown serologically. Fig. 2 shows that all normal children with this infection produced a significant rise in the titre of complement fixing antibodies, compared with only 2 out of the 7 children with ALL. However, the situation with regard to other viruses is not as obvious and that for measles is complicated by the administration of pooled immunoglobulin. Borella and Webster (1971) reported impairment of the immune response to viral infection in patients with leukaemia. Bosu *et al.* (1975) studied the antibody response to polio virus immunisation in children with leukaemia and demonstrated a uniform failure of IgM response which they felt was independent of the leukaemia treatment, since it was still present in children in whom treatment had been stopped for at least 6 months.

The diagnosis of a viral infection has in the past depended to a large extent upon the demonstration of a rise in the titre of specific antibodies. The antibody rise which occurs in normal children may not occur in children with leukaemia, and this may have resulted in the past in the failure to recognise the true importance of virus infections in leukaemia.

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Bacteriological monitoring of unheated human milk

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SUMMARY To assess the bacteriological quality of unpooled expressed breast milk, a pilot bottle sample of each donation was examined before the milk was given to the neonate. Provided the milk did not contain >2500 organisms/ml or potential pathogens it was used unheated. Milk containing between 2500 and 5000 organisms/ml and no potential pathogens was used after pasteurisation. Using these criteria, 67% of 460 donations were acceptable. However, because the bacteriological quality varied, 45% of domiciliary donations were discarded compared with only 29% of those from hospital.

Breast milk composition differs from cows' milk and artificial formulae in many important aspects. Some of these were described in the report from the Department of Health and Social Security (1974) which recommended that breast feeding should be encouraged. While human milk is generally accepted as ideal nutrition for term neonates, the composition varies and may not represent optimal nutrition for preterm infants and those of low birthweight. Davies (1977) showed that such infants fed artificial formulae had better rates of growth than those fed expressed breast milk. Nevertheless the importance of human milk to the young infant derives not only from its nutrient content but also from its 'anti-infective' properties. Lactoferrin, an iron-binding protein, is important in the prevention of infection by *Escherichia coli*; B_{12} and folate-binding proteins which limit the availability of these vitamins for bacterial growth are also important. Specific IgA immunoglobulin acts in the neonatal gut and limits the growth and reproduction of bacterial and viral pathogens. Maternal antibodies, cellular content, bacteriostatic enzymes, lysozyme, and nonpathogenic bacteria further contribute to the anti-infective properties of human milk.

Carefully controlled pasteurisation reduces the damage to the humoral components of human milk, whereas higher temperatures not only destroy vegetative bacteria but can adversely affect the anti-infective properties and alter the chemical composition of the milk (Ford *et al.*, 1977; Williamson *et al.*, 1978).

In 1976 it was decided to examine the possibility of providing unheated, unpooled human expressed breast milk at this hospital for the nutrition of low birthweight babies, especially neonates in the intensive care unit, provided the bacteriological quality met our standards. Our experience of the bacteriological monitoring and provision of raw human milk is described.

Materials and methods

Only mothers who were free of communicable disease (for example, tuberculosis, respiratory infection, enteric, skin, or breast infection) and those not on drugs transmissible via breast milk were accepted as donors.

During a 2-year period (1976–78) samples of expressed breast milk (EBM) from hospital and from women at home were examined. All mothers received instruction on breast and hand hygiene and on the technique of manual expression of the breast, although most hospital specimens were obtained by the breast pump. After the EBM had been collected into autoclaved 100 ml glass bottles, approximately 2 ml milk was decanted into a sterile pilot bottle for bacteriological screening (Fig. 1). Those specimens collected in hospital were deep frozen to −20°C in the breast milk bank freezer as quickly as possible, often within a few minutes of collection. Specimens from home were stored in the ordinary compartment of the domestic refrigerator (not deep frozen) and taken to the breast milk bank in an insulated cool box every 48 hours by the donors themselves or by domiciliary midwives. On receipt at the hospital milk bank these domiciliary donations were then also stored at −20°C. Each bottle was stored separately and *not* pooled before freezing. Donations varied in volume between 50 and 100 ml

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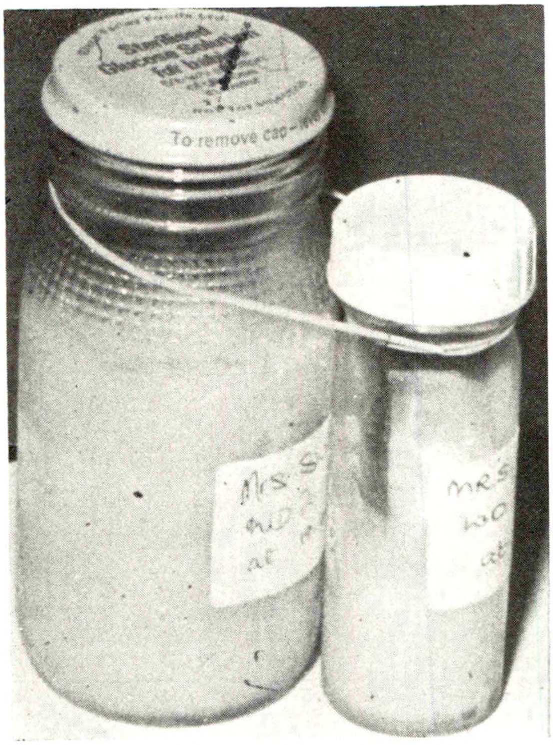

Fig. 1 *Expressed breast milk donation with accompanying pilot bottle sample.*

and did not remain in the bank for more than a few days because of the demand for human milk. Before milk was issued, the pilot bottle was removed, allowed to thaw at room temperature, and then bacteriologically screened. This usually took less than 24 hours and no raw specimen of breast milk was used until bacteriologically acceptable. When clearance was given the donation was allowed to thaw at room temperature and issued for feeding. Thawed specimens were stored in the domestic compartment of the refrigerator in the intensive care unit until needed. Any thawed specimen not used after 12 hours (although rare) was discarded to reduce risk of bacterial contamination and denaturation.

The pilot bottle of milk was examined soon after receipt in the laboratory. Total quantitative bacterial counts on unheated samples were performed in duplicate using 10 drops from a standard 50-dropper pipette on a 1 in 5 dilution of milk in 1 in 4 strength Ringer's solution, whereas pasteurised milk was examined undiluted to increase the chance of isolating organisms which would be present in smaller numbers than in unpasteurised milk. In both instances, the milk was inoculated on to 10% horse blood agar, MacConkey agar, 0·03% cetrimide agar, and nutrient agar containing 8·5% sodium chloride to facilitate the screening of organisms potentially detrimental to the safe use of milk. The sensitivity of the quantitative method meant that the minimum bacterial count detectable in unheated milk was 25 organisms/ml and in pasteurised milk it was 5 organisms/ml. Arbitrary criteria applied to the EBM samples were: (1) Milk with a quantitative count of <2500 organisms/ml (Wright, 1947) (consisting of, for example, micrococci, *Staphylococcus albus*, 'viridans type' streptococci, or diphtheroids which were considered to be contaminants probably derived from skin flora but unlikely to be pathogenic) was used unheated. (2) No donation was used unheated or pasteurised if the pilot bottle gave either a total count >5000 organisms/ml or any detectable potential pathogen. On an arbitrary basis the potential pathogens were defined as *Staphylococcus aureus*, β-haemolytic streptococci, *Pseudomonas* spp., *Proteus* spp., *Streptococcus faecalis*, and any other organism from a potential enteric or water-borne source (here defined as 'coliforms' for convenience). (3) No donated milk with a total bacterial count of 2500–5000 organisms/ml was used unheated. If the pilot sample had a bacterial count in this range, but none of the organisms listed in (2), the donated milk was pasteurised at 63°C for 30 minutes in a water bath and subjected to the same bacteriological screen, plus the alkaline phosphatase test. (Alkaline phosphatase is destroyed by a temperature of 63°C within 30 minutes and is used as evidence of adequate pasteurisation of cows' milk). Provided effective pasteurisation was established by no detectable growth on culture and a satisfactory phosphatase test, the milk was issued for use.

Results

The overall distribution of the bacterial counts of the EBM over the 2-year period is shown in Fig. 2. Clearly most EBM samples had low counts and the distribution shows gradually diminishing numbers of specimens up to 36 000 organisms/ml. Although there were 33 (4·5%) specimens with counts >50 000 organisms/ml, most (95·3%) specimens gave counts of <25 000 organisms/ml. A pilot investigation of anaerobic culture gave no additional information and was therefore stopped.

Of 688 raw EBM samples examined during the period, 513 (75%) came from hospital and 175 (25%) were domiciliary donations (Table 1). Within the three ranges of bacterial counts the figures for hospital and domiciliary isolates were similar—that is 460 (67%) of EBM samples gave counts of

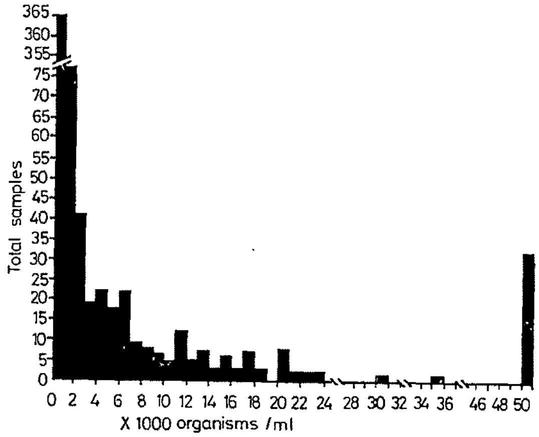

Fig. 2 *Distribution of bacterial counts in expressed breast milk over a 2-year period (1 May 1976– 30 April 1978.*

Table 1 *Pattern of bacterial counts among hospital and domiciliary donations of expressed breast milk*

Source	*Bacterial count/ml*			
	<2500	2500–5000	*>5000*	*Total*
Hospital	343 (67)	51 (10)	119 (23)	513
Domiciliary	117 (67)	15 (8·5)	43 (24·5)	175
Totals	460	66	162	688

Percentages are given in parentheses.

Table 2 *Potential pathogens isolated from expressed breast milk samples*

Organism and source	*Bacterial count/ml*			
	<2500	*2500–5000*	*>5000*	*Total*
S. aureus				
Hospital	15	5	3	23
Domiciliary	4	0	1	5
Coliform bacilli				
Hospital	8	2	11	21
Domiciliary	6	5	21	32
Pseudomonas spp.				
Hospital	0	0	1	1
Domiciliary	0	0	0	0
Faecal streptococci				
Hospital	0	0	0	0
Domiciliary	14	3	2	19
β-haemolytic streptococci				
Hospital	1	0	0	1
Domiciliary	3	0	1	4
Proteus spp.				
Hospital	0	0	3	3
Domiciliary	0	0	0	0
Totals	51	15	43	109

Table 3 *228 discarded expressed breast milk donations because of unsatisfactory qualitative and quantitative results*

*Counts >5000/ml (n = 162)**		*Potential pathogens (n = 66)**	
Hospital	*Domiciliary*	*Hospital*	*Domiciliary*
119	43	31	35

*Allowance has been made for 43 specimens discarded which had excessive counts and potential pathogens.

<2500 organisms/ml, and 66 (9·6%) specimens gave counts of 2500–5000 organisms/ml and were pasteurised if no pathogen was present. Overall 162 (24%) were immediately discarded without pasteurisation because of counts >5000 organisms/ml. Therefore, 526 (76%) EBM specimens had acceptable quantitative bacterial counts, but some of these had potential pathogens. The main pathogens isolated were *S. aureus* and 'coliforms', but there was a difference in the total number of isolates and in the type of organism from home and hospital donations. Altogether 49 (9·6%) of 513 donations from hospital were discarded, compared with 60 (34%) of 175 from homes. *S. aureus* was isolated from 23 (4·5%) of hospital donations and from 5 (3%) of home donations, whereas 'coliforms' were isolated from 21 (4·1%) of hospital and from 32 (18%) of domiciliary collections. There was no particular relationship between quantitative counts and potential pathogens, and overall the pathogens were distributed throughout the three quantitative ranges (Table 2).

Of the EBM donations with counts in the ranges of <2500 and 2500–5000 organisms/ml, 51 (7·4%) and 15 (2·2%) of them respectively had potential pathogens and were discarded without further processing. Another 43 (6·3%) were discarded because they had excessive bacterial counts and potential pathogens.

The total number of EBM donations discarded because of excessive bacterial counts or the presence of potential pathogens was 228 (33%) (Table 3). The remaining 460 (66%) were acceptable because they contained no potential pathogen or excessive bacterial counts, as defined above, within the technical limitations of the methods employed.

Discussion

Like others, we experience difficulties in deciding what bacteriological criteria should be adopted to make EBM donations safe to give to neonates. We adopted arbitrary criteria based on such information as we could obtain. There appeared to be no widely agreed standards on the quantitative and qualitative content of human breast milk and no universally adopted figure for acceptable bacterial quality of EBM. There are no general guidelines on what are considered to be potential pathogens and the likely numbers of such species which are considered harmful to neonates. There are opposing views on the benefits conferred on babies fed raw or pasteurised milk as well as conflicting results on babies fed artificial milk as opposed to EBM.

Nevertheless we decided to investigate the quantitative and qualitative bacteriology of EBM submitted to our maternity unit. It is not possible to give precise ranges of acceptable counts or to investigate which organisms constitute an unacceptable hazard to neonates, particularly those undergoing intensive care. The criteria we adopted, although arbitrary, were necessarily stringent in order to protect our neonates from any hazard of milk-borne bacterial disease. Even with these strict criteria we were still able to issue 67% of donated EBM, a figure similar to that of Williamson *et al.* (1978). Overall only 29% (150 of 513) of hospital donations were discarded compared with 45% (78 of 175) of domiliciary collections because their bacteriological quality was either quantitatively or qualitatively unacceptable. We feel that probably the collection procedure of the domiciliary EBM was the main cause for 45% of samples being unacceptable. If the donation was unsatisfactory the donor was again visited and given further advice about hygiene by the domiciliary midwife. To some extent this was done in the case of unsatisfactory hospital donations but an additional factor was the inadequate cleaning of the breast pump and related equipment. This defect was also noted by Liebhaber *et al.* (1978) who recommended manual expression of milk, thereby reducing the need for pasteurisation. Our figures also reflect the difference caused by lack of supervision of domicilary collections, and if a neonatal unit relies heavily on domiciliary donations, closer supervision is necessary or it may be advisable to pasteurise all domiciliary donations. We should stress that our policy was devised to control the quality of the EBM and the whole procedure of collection, storage, etc. up to the time of feeding the neonate. The use of the pilot bottle provided us with a representative sample of EBM. We feel that if the donations had been pooled, even after being bacteriologically cleared, it would have added another factor to the procedure, with its attendant risks.

We did not attempt to assess the immunological or the nutritional benefits of using unpooled, unheated EBM, but we did try to assess clinically whether there was any hazard of infection. Clearly this is arbitrary, but we did not detect evidence of infection due to any of the organisms considered above in any baby fed EBM. We believe this was because EBM with potential pathogens was not used and also because EBM containing by definition nonpathogens <2500 organisms/ml does not expose the baby to any risk. In fairness it should be said that if any baby is ill because of infection by an alleged nonpathogen (referred to earlier), it is extremely doubtful if the source of these ubiquitous organisms could be identified since they do not have a generally reliable marker system.

As a result of our experience in collecting and monitoring EBM, we have decided to continue to rely on raw EBM by fostering good hygiene technique which in most specimens yields low bacterial counts (Fig. 2). As a further safeguard, bacterial monitoring will exclude any donation of unsatisfactory quality. The development of this policy resulting from the ever pressing demand in our neonatal unit for EBM has led us to review our criteria in the light of these results and of other published work. We have considered the possibility of relaxing the quantitative criteria alone so that donations with higher bacterial counts (that is, those with >2500 organisms/ml) but no potential pathogens could be safely used. There is currently no generally agreed upper quantitative limit of likely nonpathogens, although most workers agree that it is inadvisable to use EBM containing potential pathogens. Ikonan and Maki (1977) used donations with counts <20 000 organisms/ml (some after heating) and discarded only 5% of all donations. If we had applied these criteria to our results in Fig. 2 we would have discarded only 10% of EBM donations on a quantitative basis alone. We are unwilling to accept EBM donations containing potential pathogens as we feel these could present unnecessary hazards to a vulnerable group of babies, particularly those undergoing intensive care. Milk containing bacteria which may be derived from a faecal origin is clearly unacceptable and these markers are used to exclude the possibility of contamination by enteric bacteria and viruses.

Breast feeding by a mother of her own normal baby will expose that baby to his own mother's bacterial flora which quantitatively may be >2500 organisms/ml, some of which may be potentially pathogenic. It is believed by some that these are probably less hazardous than the organisms from an unrelated milk donor, because a mother secretes antibodies in her milk which reflect her own immunological experience (Gunther, 1978).

As a result of the renewed interest in breast feeding and breast milk banks, attention has been given to the advantages and disadvantages of processing EBM. Because of the fear of contaminating EBM, attention has been directed to measures which provide a bacteriologically safe milk which still retains its immunological properties (*British Medical Journal*, 1977). However enterotoxins produced by certain bacteria—for example, *S. aureus* have caused outbreaks of food poisoning due to contaminated cows' milk (Wilson and Miles, 1975)—and since the enterotoxin is to some extent heat resistant it is theoretically possible that even pasteurised human milk, although free from bacteria, may contain enterotoxin.

In addition, because the alkaline phosphatase of human milk is 40 times lower than cows' milk (Heyndrickx, 1962) the phosphatase test as applied to the latter may not be sufficiently sensitive as an indicator of adequate pasteurisation of EBM. Therefore, although rigidly controlled conditions safeguard the pasteurisation process, bacteriological quality control criteria can provide a final check of effective pasteurisation.

Milk rendered safe by boiling or even by carefully controlled pasteurisation appears to reduce levels of immunoglobulin, lactoferrin, lysozyme, and complement C3 factor (Ford *et al.*, 1977; Evans *et al.*, 1978), as well as certain nutrients (Williamson *et al.*, 1978), although Raptopoulou-Gigi *et al.* (1977) in Edinburgh found that pasteurisation did not materially alter levels of IgA or lactoferrin. Total lymphocyte counts were also significantly decreased after pasteurisation (Liebhaber *et al.*, 1977). These findings indicate the reduction of anti-infective properties of EBM with pasteurisation, and by avoiding this procedure we feel that unheated EBM of acceptable bacteriological standard provides a practical alternative for a baby in place of its own mother's milk. However, in spite of the advantages of the immunological content of nonpasteurised EBM we agree with Lucas *et al.* (1978) that it cannot be recommended for all special care baby units unless there are certain quality control safeguards.

Milk macrophages tend to adhere to the walls of the glass container and therefore simple storage may reduce the lymphocyte content. Moreover, Pitt (1976) suggested that freezing of milk will markedly diminish the number of viable cells and it must be admitted that either of these factors could have reduced the effective immunological value to our babies. Quantitative examination of the noncellular components of milk deep-frozen for 3 months at −20°C had no appreciable effect on levels of lactoferrin, lysozyme, IgG, IgA, or C3 complement component (Evans *et al.*, 1978). Repeated freezing and thawing would be expected to lead to reduction of these levels because of denaturation, but in our milk bank the process only happens once.

While cellular transfer in the breast milk from the natural mother may confer immunological advantages to her baby, it may be potentially harmful in an unrelated baby. Beer and Billingham (1975) reported a wasting syndrome similar to a graft v. host disease when neonatal rats were fed on the milk of an unrelated rat. Further work is needed to find out if this observation is important to human studies on unheated EBM.

We thank Professor Rosalinde Hurley of Queen Charlotte's Hospital for her help, the hospital and district midwives for their assistance, and Ms Angela Parry for clerical assistance.

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Lost to follow up

A study of nonattendance at a general paediatric outpatient clinic

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SUMMARY 50 children defined as persistent outpatient nonattenders were compared with 50 children who regularly attended the same clinics. Several factors were more often found in the group of nonattenders: (a) initial referral via casualty without a letter from the family doctor, (b) hospital admission before the first outpatient appointment, (c) recognition of multiple medical problems, and (d) evidence of diffuse social problems affecting the family. 34 of the nonattenders had at least 2 of these factors, compared with only 9 children in the other group. Many of these problems can be identified at the initial consultation, and perhaps other methods of continuing health care should be provided for these children.

One traditional way that continuing paediatric care is given is by way of a hospital outpatient department, but nonattendance at such clinics is common (Drachman *et al.*, 1969; Alpert *et al.*, 1970; Anderson *et al.*, 1971).

This study examines the problem of nonattendance at a general paediatric outpatients department and investigates whether the persistent nonattenders form a clearly defined group. The clinics from which the patients came were those held in the main outpatient department of a busy teaching hospital serving a typical inner city area with poor social and environmental conditions, a high rate of unemployment, and a large immigrant population. Within the hospital there is a paediatric casualty department and traditionally this is seen by the local population as a source of primary health care. The study was performed at a time of year, April to June, when neither poor weather conditions nor holidays could be blamed for a low attendance.

Patients and methods

During the study period 600 appointments were made for children at Guy's Hospital general paediatric outpatient clinics. These clinics took place on Wednesday, Thursday, and Friday mornings each week. The overall nonattendance rate was 25%. About one-third of these were persistent nonattenders defined as those children who failed to attend on a particular day, who had been given at least 4 appointments, and failed 2 consecutive appointments, or more than 25% of them. Most nonattenders came from Lambeth, Southwark, or Lewisham AHA (T), and this study was restricted to children whose families were resident in these areas. A group of 50 nonattenders was compared with a group of 50 regular attenders. The regular attenders had been given appointments on the same days as the nonattenders, and had previously been given 4 or more appointments, attending more than 75 % of them, and never missing 2 consecutive appointments.

Information about the children was obtained from hospital records including neonatal, paediatric, casualty, and social work notes. We obtained information about social and family background, and looked in detail at the child's medical history, and at the family's current and past social problems. If appropriate, further information was obtained from the Social Services Department, the Community Health Services, or directly from the parents. Several home visits were made to gain further information and to discuss possible reasons for nonattendance.

Statistical evaluation was carried out with the χ^2 test.

Results

Child.

Sex

There were 32 boys in the group of nonattenders compared with 30 in the control group.

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Age

There was little difference between the ages in the two groups. Nearly half the children in both groups were under 5 years.

Length of follow-up

The length of follow-up varied from a few months to several years. The slightly higher proportion of nonattenders (64%) followed up for less than 12 months, compared with 42% in the other group did not reach statistical significance ($\chi^2 = 4{\cdot}86$, $P>0{\cdot}02$).

Family background

Social class

In both groups most of the families were in social class IV or V (Registrar General's classification). There was little difference between the numbers of unsupported mothers in the two groups. However, all the 6 unemployed fathers belonged to families of nonattenders (Table 1).

Ethnic group

24% of nonattenders and 12% in the control group had parents whose country of origin was outside the United Kingdom and Ireland (Table 2).

Housing

70% of families in both groups were living in local authority housing. This is only slightly higher than the rate for the local population.

Family structure

The families of both groups were of similar sizes (Table 3). There were 124 children in the families of nonattenders and 126 in the other group (Table 4). The control group families appeared to have a higher proportion of children over age 16 years: 22% compared with 13%. Three nonattenders and 2 children in the control group each had 2 siblings under 5 years.

Table 3 *Number of children in family*

Group	*No. of children*			
	1	*2*	*3*	*4 or more*
Nonattenders	16	12	11	11
Control	12	18	7	13

Table 4 *Ages of children in family*

Group	*0–5 years*	*6–15 years*	*16 years*	*Total*
Nonattenders	38	70	16	124
Control	32	66	28	126

Contact with the hospital.

Method of referral

For 64% of the nonattenders the initial contact with the hospital had been in the casualty department without a referring letter. Significantly fewer (22%) of the control group presented in this way ($\chi^2 = 17{\cdot}99$, $P<0{\cdot}001$). The casualty attendance led to the child being admitted for 25 nonattenders and 6 control children. The majority (64%) of the control group had been referred to the hospital by their family doctors and, with the exception of 2, directly to the outpatient department.

The routes of initial referral to outpatients are summarised in Table 5. Far more (50%) of the nonattenders had their first outpatient appointments made as the direct result of admissions to hospital ($\chi^2 = 11{\cdot}57$, $P<0{\cdot}01$).

Initial referral diagnosis

There was no great difference between the two groups in the reason for referral. More than 30% of

Table 1 *Social class**

Group	*Nonmanual*	*Manual*	*Others†*	*Unemployed*	*Unsupported*	*Not known*
Nonattenders	6	16	2	6	8	12
Control	10	24	1	0	10	5

*Registrar General's classification, father's occupation.
†For example, the Forces.

Table 2 *Ethnic group*

Group	*UK/Irish*	*W. Indian*	*African*	*Indian subcontinent*	*Cypriot*	*Far Eastern*	*N. African*	*Mixed*
Nonattenders	38	4	0	2	3	0	1	2
Control	44	4	1	0	0	1	0	0

Table 5 *Method of referral*

Group	*Casualty*	*Casualty and ward*	*GP*	*GP and ward*	*Labour ward*	*Other hospital*
Nonattenders	7	25	15	0	3	0
Control	5	6	30	2	3	4

children in both groups were referred because of respiratory tract disorders. 13 nonattenders were admitted with respiratory tract disorders compared with only 3 children in the control group.

Subsequently identifiable problems
During the period of hospital contact 22 nonattenders were recognised as having further medical problems, compared with only 8 children in the other group ($\chi^2 = 9\cdot33$, $P<0\cdot01$). Nearly half of these problems were either of a psychiatric or a psychosocial nature—for example behaviour problems, enuresis, school refusal.

Of the 22 children with subsequently identifiable problems, 5 were found to have multiple problems during the follow-up period. For example, one child was first seen in outpatients department after hospital admission for an episode of wheezy bronchitis at age 4 months. During the period of intermittent attendance further problems became apparent: failure to thrive, behaviour problems, and the possibility of child abuse.

Hospital admissions
There was no difference in the number of hospital admissions for the two groups of children during the period of outpatient follow-up. More than 40% of children in both groups were admitted to hospital during this period. Of these, about a quarter had at least 4 admissions.

Casualty attendance
60% of nonattenders and 62% of the control group did not visit the casualty department during the last 3 years of follow-up. 8% in both groups made at least 10 visits.

Growth
There was no difference in the weight or height of the children in either group. Approximately 15% of children were <10th centile for either height or weight.

Neonatal concern
Records were examined to see if any medical concern had been noted in the neonatal period—for example admission to a special care baby unit, low birthweight, prematurity, prolonged jaundice, apnoeic attacks.

Although there was a suggestion that more nonattenders (14) had neonatal problems than control children (9), this was not significant.

Contact with social services.

74% of families from the group of nonattenders were known to the social services, either within the hospital or in their local area, during the period of follow-up. Many were actively concerned with the social services at initial referral. Only 38% of families from the control group were in contact with social services ($\chi^2 = 13\cdot15$, $P<0\cdot001$).

Social work problems can be divided into defined and diffuse (Lynch *et al.*, 1976). Defined problems are isolated ones in otherwise stable families—for example housing, practical help with the care of the children, assistance with the emotional difficulties of the child's illness. Diffuse problems are those in which a number of long-term problems beset the whole family. For example, one family was being helped by the social services because of poor housing conditions. However, it soon became apparent that there were numerous other problems. The father had been unemployed for 2 years, there were massive rent arrears, a sibling of the nonattender was a school refuser, and when one of us (N.A.C.) visited the family he found the outpatient appointment cards propping up the hi-fi record deck.

Using this classification, families known to social services were allocated to either a defined or diffuse category. 78% of the families of nonattenders and 42% of the control group receiving social work help were considered to have diffuse social problems ($\chi^2 = 7\cdot37$, $P<0\cdot01$). Thus 58% of all the children who were nonattenders came from families who had diffuse social problems while only 16% of the control group came from such backgrounds ($\chi^2 = 18\cdot98$, $P<0\cdot001$).

Two of the children in the group of nonattenders were on the 'at risk' register at the time of failed follow-up.

Adverse factors.

Four factors were significantly more often present in the group of nonattenders: (a) initial referral via casualty, without a letter from the family doctor, (b)

Table 6 *Total number of adverse factors*

Group	*0*	*1*	*2*	*3*	*4*
Nonattenders	8	8	13	12	9
Control	30	11	6	2	1

hospital admission before the first outpatient appointment, (c) recognition of multiple medical problems, (d) evidence of diffuse social problems affecting the family. The distribution of these factors is shown in Table 6. There is a pronounced accumulation of 'adverse' factors in the group of nonattenders, 34 children having at least 2. Only 9 control children had more than one factor.

Discussion

American studies suggest that nonattendance at outpatients departments is common (Drachman *et al.*, 1969; Alpert *et al.*, 1970; Anderson *et al.*, 1971). It would seem that this is equally true here in an inner-city area, with 25% of appointments not being kept. However, this is still better than the nonattendance rate in general paediatric clinics in the USA, where 40% of appointments are missed (Anderson *et al.*, 1971). One-third of the nonattenders at the Guy's clinic persistently failed to appear. This persistent failure to attend was unrelated to the child's age, sex, ethnic origin, or the family's social class. However, all the children with unemployed fathers were nonattenders.

A large young family is likely to make it more difficult for a parent to bring a child to the outpatients department. While there were no fewer preschool siblings in the control group, there was a suggestion that overall these families, while being of similar size, were older as 22% had at least one child over age 16, compared with 13% in the families of nonattenders. Unfortunately parental ages were not always recorded but it may well be that the parents of persistent nonattenders were younger and less experienced. Many of the nonattenders (64%) were referred from casualty without referral letters from their family doctors, and half of them were admitted to hospital before their first outpatient appointments. This suggests that these parents only seek urgent medical advice when their children have acute illnesses. The fact that many of the diagnoses on admission were of illnesses often treated at home—for example otitis media, upper respiratory tract infections, mild wheezy bronchitis—suggests that other factors may have influenced the decision for admission. In a recent survey in Nottingham, lack of home facilities and parental capacity was judged to be the main factor in the decision to admit a child in 20% of cases (Wynne and Hull, 1977).

Although the initial diagnoses were similar in the two groups, there was evidence that the families of nonattenders subsequently developed multiple problems of both a medical and psychosocial nature. Although unrecorded at the time it seemed that many of these problems were present at the initial referral.

The children who persistently failed to attend not only had multiple medical problems, but also came from families with diffuse social problems (58%). Many of these children were already known to the social services at the initial referral, and this may have influenced the decision to admit to hospital when first seen in the casualty department.

Many of the nonattenders needed continuing health care, as shown by the number of admissions to hospital during the follow-up period. This was very similar in both groups with 10% of children requiring at least 4 admissions.

It appears from the evidence presented in this study that children who persistently fail to attend outpatients form a definable group. They tend to have diffuse medical and social problems, and their parents tend to view minor acute illnesses as requiring urgent medical attention, yet fail to seek long-term medical care. There is a need to explore other ways of providing health care for children whose parents persistently fail to bring them to hospital for follow-up.

It has been suggested that if a visit is made to the home shortly before the hospital appointment the child is more likely to attend, but this appeared to be partly related to providing transport to the hospital (Anderson *et al.*, 1971). Of 12 families visited at home in this study, none viewed transport as a major obstacle to their ability to attend, and indeed many resided within easy walking distance of the hospital. A social worker could well help to plan the family's visit to the hospital and might improve attendances and give a valuable opportunity for a joint discussion of the family's interrelated medical and social problems.

It has been shown that nonattenders at community child health clinics are similar to those described here (Ford, 1976). However, in this sample several families attended child health clinics or used a day nursery although they failed to use either hospital services or their family doctors on a regular basis. Follow-up might well be successfully carried out in the community with help from the health visitor and social worker. A united effort by both community and hospital services to encourage parents to take their children to a single clinic is likely to be much more successful than uncoordinated attempts to make them attend a variety of different agencies.

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The following articles will appear in future issues of this journal:

Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children: anticonvulsant effect and side effects. *F. U. Knudsen.*

Water loss from the skin of term and preterm babies. *N. Rutter and D. Hull.*

Family resemblances of height, weight, and body fatness. *L. J. Hawk and C. G. D. Brook.*

Ethnic differences in the Goodenough-Harris draw-a-man and draw-a-woman tests. *A. E. Dugdale and S. T. Chen.*

Should we follow up children with Henoch-Schönlein syndrome? *J. C. Coakley and T. L. Chambers.*

Accuracy of pre- and postnatal assessment of gestational age. *D. Mitchell.*

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Oral fat loading test

A reliable procedure for the study of fat malabsorption in children

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SUMMARY Oral triglyceride (TG) loading tests were performed in four groups of children: normal controls, patients with chronic nonspecific diarrhoea (CND), biopsy-proved mucosal pathology (MP), and disturbed intraluminal fat malabsorption (IFM). The rise of plasma TG levels ≥ 55 mg/100 ml ($\geq 0\cdot6$ mmol/l) can discriminate between patients with gastrointestinal disease and normal controls or patients with functional disturbances. The postmeal plasma TG rise correlates well with the coefficient of fat absorption (CFA) in normal subjects, patients with CND, and patients with IFM, but not in patients with MP who showed a disproportionally low plasma TG rise compared with their CFA. This test can serve as a useful tool in diagnosis and clinical evaluation for children with gastrointestinal disorders.

The evaluation of fat absorption is based mainly on balance studies, measuring intake and output over a particular period. The technical difficulties, especially that of reliable stool collection, have limited the use of this method. Other techniques using loading tests of iodine-labelled (Barbieri *et al.*, 1968) or ^{14}C-labelled fat (Shigekoto and Wagner, 1968) depend on accurate urine or expired air collections and pose similar problems. Plasma triglyceride (TG) increase after oral fat load has been found useful in evaluating fat malabsorption in children with a variety of gastrointestinal diseases (Norman *et al.*, 1971; Fällström *et al.*, 1977). The reliability of this method to determine various degrees of fat malabsorption has not yet been investigated, nor has this method been used in children with chronic nonspecific diarrhoea (Davidson and Wasserman, 1966).

We used the oral fat load to evaluate the correlation between the rise in plasma TG after a test meal and the coefficient of fat absorption in various disorders, including that of chronic nonspecific diarrhoea.

Patients and methods

21 children with no gastrointestinal symptoms aged between one month and 14 years were compared with three groups of patients: (a) 14 children aged between 5 months and 8 years with chronic nonspecific diarrhoea (CND) and normal or transiently delayed weight gain, in whom no gastrointestinal disease could be shown; (b) 17 patients aged between 4 months and 14 years with biopsy-proved intestinal mucosal pathology (MP). This group comprised 13 patients with gluten-sensitive enteropathy, and 4 babies with postgastroenteritis malabsorption; (c) 12 patients aged between one month and 8 years with intraluminal fat malabsorption (IFM), This group comprised 7 patients with cystic fibrosis and 5 children with bacterial overgrowth as shown by duodenal fluid culture.

Fat was determined on 72-hour stool collections using a gravimetric method (Jeejeebhoy *et al.*, 1970). In small children stools were collected with the aid of metabolic frames. Fat intake was measured during the collection period and the coefficient of fat absorption (CFA) calculated according to the formula: (fat intake − fat output) × 100/fat intake. The TG loading test was performed after a 6-hour fast in small children and after a 12-hour fast in older ones. The meal consisted of Blue Band margarine, 2 g/kg, mixed with cocoa powder and saccharine, to form a cream of acceptable taste. The fatty acid composition of this margarine is 19·5% saturated (12%-palmitic, 7·5%-stearic), and 80·5% unsaturated (43·8%-oleic, 32%-linoleic, and 4·7%-linolenic). Small babies and reluctant toddlers were intubated. In the latter case the mixture was melted to a maximum temperature of 60°C. Blood was

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drawn at periods of 0, 2, and 4 hours after fat ingestion. Plasma TG levels were determined fluorimetrically using a Technicon AAII (Kessler and Lederer, 1965).

Results

Fasting plasma TG levels varied widely and there was no difference between the groups. Two hours after ingesting the test meal, both control and CND groups showed a constant and significant rise in plasma TG (Table). Although the patients with CND had lower levels than controls, they were clearly distinct from both groups with IFM and MP who showed a slight rise in plasma TG levels. Fig. 1 shows the 2-hour rise of plasma TG in each patient. None of the children with gastrointestinal disease showed a rise >40 mg/100 ml (>0·4 mmol/l). Of the 29 patients studied, 11 had no rise at all and some even had a decrease in plasma TG values. They differed significantly from controls and patients with CND who exceeded a slight rise of 55 mg/100 ml. The only exception, a 4-year-old child with recurrent diarrhoea, had also a borderline coefficient of fat absorption of 88% but no other evidence of gastrointestinal disease.

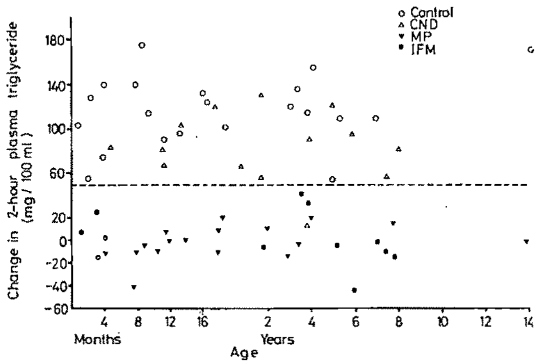

Fig. 1 *Two-hour rise in plasma triglyceride values after an oral fat load in various groups of patients. Broken line at 50 mg/100 ml separates patients with fat malabsorption from controls and those with CND.*

The 4-hour postloading TG values tended to return to preloading levels in most children and were not useful in identifying the various groups. These values are therefore not presented here.

By comparing the 2-hour plasma TG values with the CFA ones (Fig. 2), a significant correlation was obtained in controls ($R = 0{\cdot}84$ $y = -679{\cdot}21 + 8{\cdot}7 \times P < 0{\cdot}001$), CND ($R = 0{\cdot}77$ $y = -801{\cdot}1 + 9{\cdot}4 \times P < 0{\cdot}001$), and patients with IFM ($R = 0{\cdot}61$ $y = -95{\cdot}1 + 1{\cdot}3 \times P < 0{\cdot}05$). Only the MP group had a much lower plasma TG increase compared with their CFA, and accordingly no signiffcant correlation was observed ($R = 0{\cdot}47$, P = NS).

Discussion

The results of this study show that a 50 mg/100 ml (0·6 mmol/l) rise in plasma TG levels 2 hours after an oral fat load can serve as a useful screening procedure for separating children with gastrointestinal disease from controls and from children with CND. The inexpensive fluorimetric method proved adequate and gave results comparable with those using more expensive gas liquid chromatography (Fällström *et al.*, 1977). The procedure should thus be available routinely in clinical laboratories.

The good correlation between CFA and 2-hour rise of plasma TG levels in most children including normal controls, children with CND and IFM, suggest that this test is a reliable reflection of the processes of fat absorption in most conditions. Accordingly it may serve in evaluating various therapeutic measures in children with cystic fibrosis, bacterial overgrowth, and cholestasis. Patients with MP failed to show this correlation. In these conditions the greater disturbance of fat absorption in the proximal intestine is illustrated by the low 2-hour rise of plasma TG levels. The relatively higher CFA is possibly the result of some compensation brought about by absorption in distal, less involved parts of the gut. This may explain the better discriminating capacity of this test compared with

Table *Plasma triglycerides, stool fat, and coefficient of fat absorption (CFA) (means ± SD) in the various groups of children*

Group	*Plasma triglycerides (mg/100 ml)*			*Stool fat (g/24h)*		*CFA % intake*	
	Fasting	*2-h postmeal rise*	*P*		*P*		*P*
Controls (n = 21)	115·5 ± 87·8	116·0 ± 33·9	—	1·5 ± 0·9	—	94·8 ± 2·8	—
CND (n = 14)	81·4 ± 45·8	82·1 ± 31·8	<0·01†	1·6 ± 0·8	NS	95·4 ± 2·7	NS
MP (n = 17)	99·4 ± 49·0	0·6 ± 14·7	<0·01	4·0 ± 2·6	<0·01*	83·3 ± 5·5	<0·01*
IFM (n = 12)	85·8 ± 29·6	1·2 ± 24·9	<0·01	11·3 ± 8·2	<0·01	74·6 ± 11·4	<0·01

P compared with control, *compared with IFM, †compared with both IFM and MP.
Conversion: traditional units to SI—triglyceride: 1 mg/100 ml ≈ 0·0113 mmol/l, stool fat: 1 g/24 h ≈ 3·52 mmol/24 h.

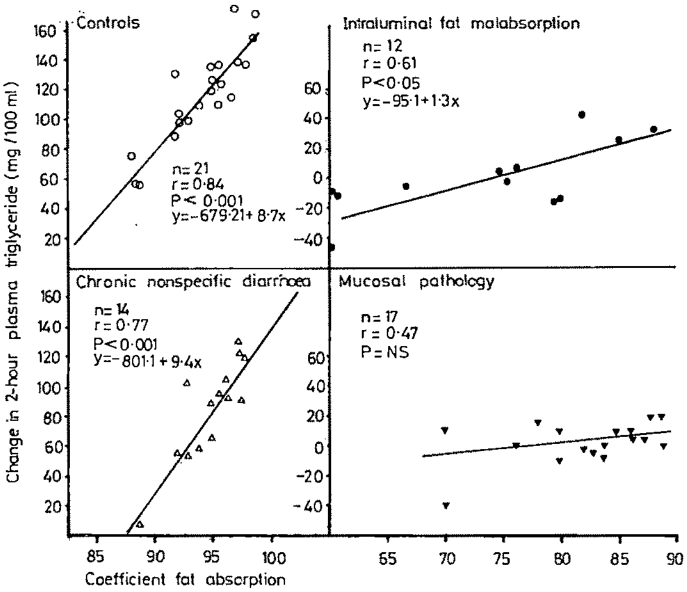

Fig. 2 *Relation between the rise in plasma triglyceride levels 2 hours after the test meal and the coefficient of fat absorption.*

faecal fat measurement in patients with gluten entropathy (Fällström *et al.*, 1977). The test may prove useful in early evaluation of gluten challenge, notably the timing of postchallenge biopsy.

Children with CND constitute the bulk of clinical material seen in most gastrointestinal services. This group demonstrated a lower increase in plasma TG levels compared with normal subjects, yet, with a single exception, they could easily be separated from patients with gastrointestinal disease. Borderline CFA had previously been reported in some of these children (Davidson and Wasserman, 1966); the significance of this observation is still not known.

We thank Mrs Y. Goldberg for the lipid determinations, Mrs R. Sandak for secretarial help, and Mrs L. Tzifroni and Mrs M. Normand for their help in preparing and feeding the meal.

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Serum cholecystokinin, basal acid secretion, and infantile pyloric stenosis

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SUMMARY The fasting serum cholecystokinin-like activity was measured in 21 infants with pyloric stenosis and in 13 normal controls. No significant difference was found between the two groups. The basal acid secretion was measured by continuously aspirating the previously emptied stomach for one hour. The basal gastric volume and the total and the free acidity were all greater in the pyloric group.

We have previously suggested that increased serum levels of cholecystokinin (CCK) may be responsible for the development and persistence of infantile pyloric stenosis (Rogers *et al.*, 1975). Infants with this condition would have inherited a greater than normal parietal cell mass and, consequently, would have gastric hyperacidity. CCK is released from the duodenum by acid stimulation (Meyer *et al.*, 1970) and causes pyloric muscle contraction (Fisher *et al.*, 1973). Antral distension due to pyloric hold-up would release gastrin with the likelihood of further acid secretion (Debas *et al.*, 1974), and hence a sequence of events leading to pyloric stenosis of infancy would result (Fig. 1). We measured the serum CCK-like activity from infants with pyloric stenosis and from normal control infants. The basal gastric acid secretion was also measured as far as was ethically possible.

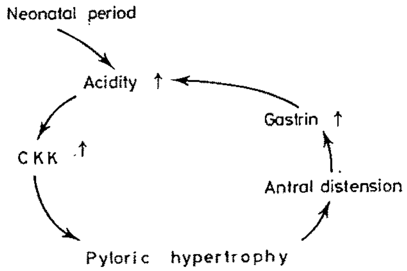

Fig. 1 *Sequence of events leading to pyloric stenosis.*

Materials and methods

21 infants with pyloric stenosis and 13 control infants were studied. The stomach was aspirated dry using a double-lumen nasogastric tube, and 3 ml peripheral blood was obtained by venepuncture. The serum was quickly separated and immediately frozen for subsequent analysis of CCK-like activity.

Serum CCK was determined by radioimmunoassay as described elsewhere (Harvey *et al.*, 1974a). The antiserum used (OC2/9) was raised against the C-terminal octapeptide of CCK (provided by Dr M. Ondetti, Squibb Institute) and used at a working dilution of 1/30 000. All samples were measured in triplicate, and samples from the paired tests in individual infants were measured in a single assay. However, as at least 3 molecular forms of CCK are present in blood and tissues (Harvey *et al.*, 1974b), and as the assay detects all 3, it was decided to categorise the CCK values into low, medium, or high range.

The gastric aspirate obtained by one hour's continuous suction was analysed for volume, pH, and free and total acidity. With the control babies the gastric analysis was performed at least 3 hours after their last feed.

This project was approved by the ethical committee of the Royal Hospital for Sick Children, Glasgow; informed parental consent was obtained in each case.

Results

Basal acid secretion. A greater volume of gastric juice was obtained from the pyloric infants. These results were highly signficant ($P<0\cdot01$) (Fig. 2).

The basal pH did not differ significantly between the two groups ($P>0\cdot1$) (Fig. 3), but the total

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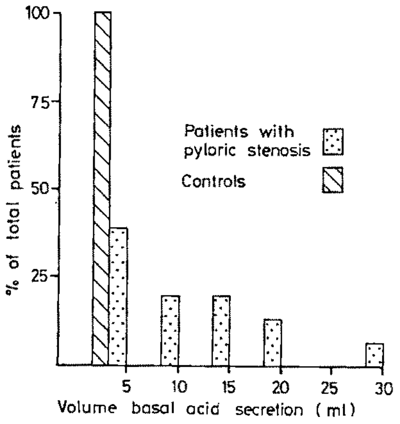

Fig. 2 *Basal acid secretion.*

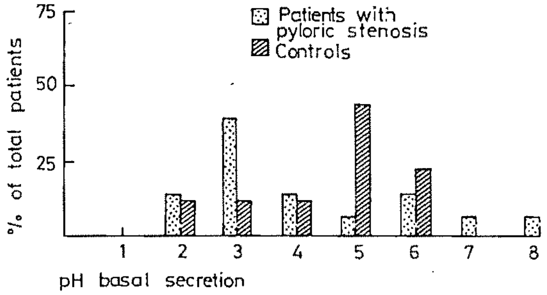

Fig. 3 *pH Basal secretion.*

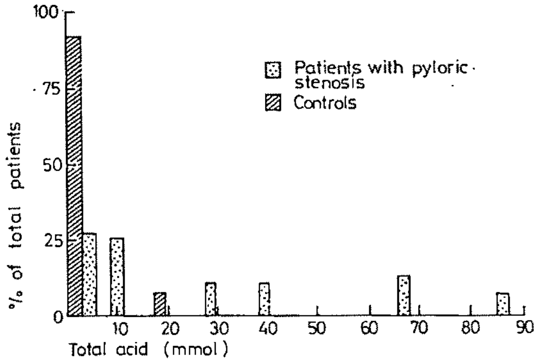

Fig. 4 *Total acidity titrated to pH* 7·4.

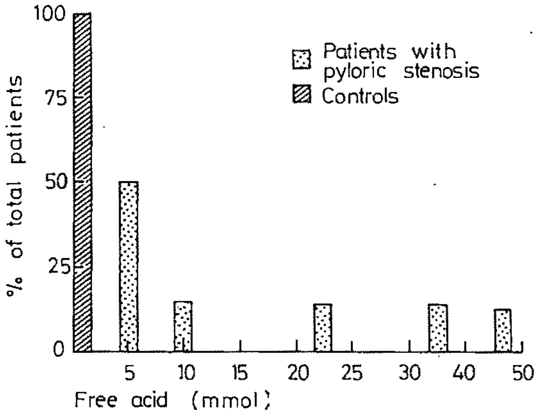

Fig. 5 *Free acidity titrated to pH* 3·5

(P<0·01) and the free acidity (P<0·05) were greater in the pyloric group (Figs 4 and 5).

None of the aspirates from the controls could be titrated to pH 3·5. This was usually because too little volume was obtained, or sometimes the starting pH was already more alkaline than pH 3·5 (Fig. 3). Hence none of these infants had measurable free acidity. Similarly in only one instance could total acidity be measured in the control group and, on that occasion, it was 19 mmol (Fig. 4).

CCK-like activity. The results obtained in both groups were generally higher than those normally found in fasted adults but due to the empirical nature of the values, this could not be verified statistically.

There was little difference in the distribution of the high, medium, or low range of CCK-like activity between the pyloric and the control group although

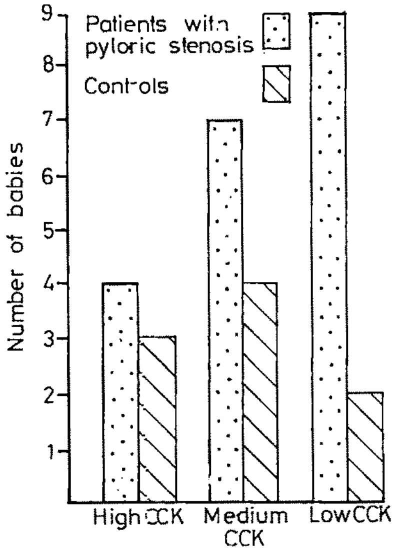

Fig. 6 *CCK-like activity.*

the pyloric group tended to accumulate more of the low range values. This tendency was not significant (Fig. 6).

In 6 infants postoperative serum samples were taken between 1 and 2 weeks after surgery. In 5 of these babies the CCK-like activity had increased to a higher range.

Discussion

The physiological basis for the development of infantile pyloric stenosis is a relatively new area of interest. It is known that the pyloric sphincter contracts *in vivo* to duodenal acidification (Fisher *et al.*, 1973) and polypeptide hormones, particularly CCK, are thought to be implicated (Isenberg and Csendes, 1972).

Our findings support the view that hyperacidity is present in infants with pyloric stenosis. This opinion presumes that no significant gastric secretion is being lost through the normal pylorus in the control infants. Our findings do not support the suggestion that increased CCK-like activity is implicated in the pathogenesis of this condition.

Our original hypothesis that hypergastrinaemia is responsible for the development and persistence of pyloric stenosis (Rogers *et al.*, 1975) has now been studied by others (Spitz and Zail, 1976; Bleicher *et al.*, 1978). Both studies confirmed the presence of hypergastrinaemia and we concede that our earlier failure to confirm hypergastrinaemia might have been due to technical considerations.

We thank M. D. Moore, biochemist, Stobhill Hospital for statistical and technical assistance, the physicians and surgeons of the Royal Hospital for Sick Children, Glasgow for allowing study of infants, and John Grant, paediatric surgeon for his encouragement and continuing interest.

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Prolonged QT interval and cardiac arrhythmias in two neonates: sudden infant death syndrome in one case

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SUMMARY Two neonates with arrhythmias and the long QT syndrome are described. The arrhythmias were detected *in utero* and both infants were apparently well after birth. The first infant, although well, had a bradycardia for the first 9 days of life. A normal heart rate was documented at 10 days but a prolonged QT interval was not appreciated on the ECG. He was discharged from hospital but died suddenly and unexpectedly 3 days later. A post-mortem examination failed to find a cause for his death which therefore fell into the category of the sudden infant death syndrome (SIDS). A retrospective analysis of the perinatal electrocardiogram showed a probable junctional rhythm with 2:1 conduction to the ventricle; the QT interval was prolonged at 0·52 seconds (QTC = 0·63). The second infant had a QT interval of 0·52 seconds (QTC = 0·54) and frequent ventricular premature beats on a 24-hour electrocardiogram. She was treated with propranolol and remains well 2 years later. Sudden infant death has often been described in the siblings of children with the long QT syndrome and one other report described a case of SIDS which was said to have had a prolonged QT interval on the perinatal ECG. This report, however, provides unquestionable evidence, in one case, of an association between the long QT syndrome and SIDS.

Cardiac arrhythmias occur frequently in the healthy newborn infant (Morgan and Guntheroth, 1965; Southall *et al.*, 1976, 1977; Ferrer *et al.*, 1977). Some of these arrhythmias may be considered a normal finding in the newborn, but others have more serious implications as similar disorders have been reported to cause sudden death in childhood (Radford *et al.*, 1977). With other authors (Guntheroth, 1977), we have already suggested a possible link between the more serious of the arrhythmias and conduction disorders and the sudden infant death syndrome (SIDS). We describe here two apparently healthy neonates with arrhythmias and the long QT syndrome. One was treated and remains well, while the other—whose death fell into the category of SIDS—was found to have this abnormality on retrospective analysis of the electrocardiogram.

Case 1

This boy, birthweight 2·5 kg, was the first child of a 23-year old woman. She did not smoke, and her home circumstances were materially good. At 37 weeks' gestation she was admitted to hospital with moderate pre-eclamptic toxaemia and treated with frusemide 40 mg once daily, slow K 600 mg twice a day, and diazepam 5 mg three times a day. During this admission the fetal heart rate was noticed to be irregular, with slowing to less than 100 per minute. At 39 weeks' gestation spontaneous onset of labour occurred, and after 9 hours a forceps delivery was carried out for pre-eclamptic toxaemia and fetal bradycardia. The pulse rate was 140/min at birth but fell to 73/min after 12 hours. The infant was clinically well and an ECG was taken and interpreted as 2:1 atrioventricular block (Fig. 1). This brady-

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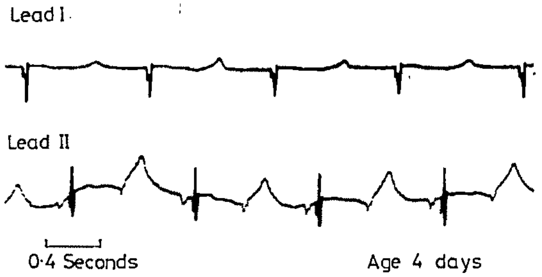

Fig. 1 *Standard ECG showing a probable junctional rhythm of 130/min with 2:1 conduction and a prolonged QT interval of 0·52 seconds (QTC = 0·63). Origin of the impulse is probably junctional rather than sinus because of the abnormal P wave axis (−90°).*

cardia persisted until 9 days of age when the heart rate reverted to 130/minute; no ECG was recorded at this time. The baby was discharged from hospital and 2 days later, while being breast fed, he collapsed and died. A post-mortem examination performed by the pathologist appointed to the Department of Health study group into SIDS failed to show an adequate cause for this death. The paediatricians who attended this infant before discharge from hospital were surprised by his death and did not consider that the transient postnatal bradycardia was responsible. A diagnosis of SIDS was therefore made by the coroner. Because of our interest in the possible association between neonatal arrhythmias and SIDS we were asked by the pathologist to review the ECG taken shortly after birth. Our interpretation was that this arrhythmia represented a probable junctional rhythm of 136/min with alternate junctional impulses failing to conduct to the ventricle because of the prolonged phase of repolarisation (a QT interval of 0·52 seconds as measured over 10 beats, QTC = 0·63). A detailed study of the conducting system of the heart was normal. The sinus node was in the expected lateral position, and was morphologically normal. The posterior atrial ganglia were related to an area of epicardial haemorrhage, but contained no inflammatory changes. The atrioventricular node was well formed, and gave rise in normal fashion to a penetrating bundle. There were slight extensions of archipelagos into the central fibrous body. The branching bundle was well formed and the bundle branches of typical morphology. No inflammatory changes were noted in the conduction tissues.

There was no family history of deafness, fainting, or sudden death, and electrocardiograms on his parents and grandparents showed normal QT intervals.

Case 2

This girl was the first child of a 22-year-old non-smoking, married woman who had emigrated to England from Pakistan 13 years previously. The mother was taking diazepam 2 mg twice daily for anxiety during pregnancy and was investigated at 28 weeks' gestation for fainting attacks. At 32 weeks' gestation a fetal bradycardia of 90/min was noticed which persisted until the time of delivery. At 39 weeks, spontaneous onset of labour occurred and a term girl weighing 2·058 kg was born. A standard electrocardiogram on the first day of life showed sinus bradycardia of 90/min and as measured over 10 beats a prolonged QT interval of 0·52 seconds (QTC = 0·54). Her serum calcium was 2·34 mmol/l (9·36 mg/100ml) and potassium 4·8 mmol/l. Subsequent electrocardiograms continued to show a long QT interval and a 24-hour electrocardiogram showed frequent ventricular premature beats (up to 40 per minute) (Fig. 2). Propranolol 1 mg 8 hourly was given and produced a pronounced reduction in the number of ventricular premature beats on the 24-hour ECG. The child is now 2 years but has a perceptive deafness. Her electrocardiogram continues to show a prolonged QT interval. She has remained well on propranolol and has never fainted. There was no family history of deafness or sudden death, and electrocardiograms on her parents have shown normal QT intervals.

Discussion

The prolonged QT interval found on the electrocardiogram in these two cases appears to represent congenital abnormalities of repolarisation. The presence of deafness in Case 2 indicates the Jervell and Lange-Nielsen syndrome (Jervell and Lange-Nielsen, 1957). Metabolic causes such as hypokalaemia, hypocalcaemia, and hypomagnaesaemia were unlikely to have been responsible for QT prolongation in Case 1 because the arrhythmia was present *in utero*.

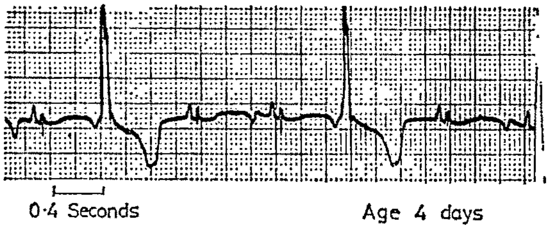

Fig. 2 *24-hour ECG showing multiple ventricular premature beats and a prolonged QT interval of 0·52 seconds (QTC = 0·54). (QRS tracings have been made darker).*

Experimental and clinical observations have suggested that the long QT syndrome may be due to a congenital disorder of the autonomic nervous system (Schwartz and Malliani, 1975; Schwartz *et al.*, 1975). While a recent study by James *et al.* (1978) demonstrated inflammatory changes in the autonomic cardiac ganglia of patients with long QT, no such changes were present in our case. It is, however, interesting to note that both mothers were taking diazepam during pregnancy. This drug is known to affect the autonomic nervous system (Dukes, 1976).

Case 1 not only had a long QT interval but also a probable accelerated junctional rhythm with 2:1 conduction to the ventricle. We suspect a junctional rather than a sinus rhythm because of the abnormal P wave axis (−90°) but an ectopic atrial focus is a possibility. We presume that alternate junctional beats failed to conduct to the ventricle because of its prolonged phase of repolarisation rather than atrioventricular node dysfunction, although we cannot exclude this latter conduction disorder. Conduction disorders probably representing sinus node dysfunction have previously been described by Olley and Fowler (1970) but to the best of our knowledge this particular arrhythmia has not been reported. An ECG was not performed when the heart rate was normal and therefore we do not know the mechanism behind this change in rate. The irregular rhythm noted before birth could have represented ventricular premature beats but none was documented on the standard ECG performed shortly after birth. In our opinion, a ventricular tachyarrhythmia associated with a low threshold for ventricular fibrillation due to the long QT interval was responsible for the sudden death of this infant, rather than asystole associated with the junctional rhythm and 2:1 atrioventricular conduction. We feel that the latter was secondary to the prolonged phase of repolarisation rather than to atrioventricular nodal dysfunction.

SIDS has been reported in siblings and other close relatives of children with the long QT syndrome (Romano *et al.*, 1963; Fraser and Froggatt, 1964; Chaudron *et al.*, 1976). Fraser and Froggatt (1964) and Schwartz (1976) suggested that some sudden unexpected infant deaths were likely to be associated with this conduction disorder. This hypothesis has however led to controversy. Maron *et al.* (1976) studied parents and siblings of cases of SIDS and found longer than normal QT intervals in some of these relatives. However, Kukolich *et al.* (1977) using similar family studies, and Kelly *et al.* (1977) in 'near-miss' SIDS cases, both failed to find significantly prolonged QT intervals. Smith (1978) has recently described a case of SIDS said to have had a prolonged QT interval of 0·32 seconds (QTC = 0·48) on a perinatal ECG but in our opinion the QT interval on the published ECG was within the normal range (Walsh, 1963). Thus Case 1 in this present study provides strong evidence to support the hypothesis that there is a causal relationship between the long QT syndrome and some cases of SIDS. As previously suggested by Schwartz (1976) and Maron *et al.* (1976), only a prospective ECG study of a large newborn population will establish the true incidence of this conduction abnormality and determine the number of sudden infant deaths associated with it.

These cases are also of interest because they were detected before birth. Ventricular fibrillation or asystole in the fetus could result in an otherwise unexplained stillbirth and it is possible that a small number of stillbirths are related to the long QT syndrome.

Despite their arrhythmias both infants were clinically well at the time of their ECGs and in our opinion it is probable that their different outcomes related to the treatment of Case 2 with propranolol. This drug has been shown to reduce the severity and frequency of syncopal episodes in the long QT syndrome (Ward, 1964; Gale *et al.*, 1970; Garza, *et al.*, 1970; Wellens *et al.*, 1972; Schwartz, 1976), possibly by reducing the incidence of ventricular tachyarrhythmias. 24-hour ECG monitoring of Case 2 showed that treatment with propranolol almost completely abolished ventricular extrasystoles.

The presence of a junctional rhythm in Case 1 might have represented an associated disorder of sinus node function. It is therefore possible that treatment with propranolol, because of its depression of automaticity and conduction (Stephen, 1966), could have precipitated dangerous bradycardias in this infant. However, a case has recently been described (Olley and Fowler, 1970), where, in this syndrome, syncope due to asystole and associated with short runs of slow junctional rhythm responded to propranolol.

The long QT syndrome is known to cause sudden death in older children. We suggest that our case of SIDS was probably due to an arrhythmia associated with this cardiac conduction abnormality. The absence of both a family history and of a prolonged QT interval in the relatives of these patients confirms that an obvious hereditary factor may not always be present. Only a large prospective study of the ECG in the newborn infant will establish the true incidence of this disorder.

We thank Dr Iain Forrest-Hay, who carried out the original post-mortem examination, for bringing Case 1 to our attention. Dr Southall is supported by a grant from the Board of Governors of the Brompton Hospital. We also thank Mrs Susan Cowley and Mrs Dorothy Lewis who typed the manuscript. The 24-hour analyser was supplied by the British Heart Foundation.

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Viruses and acute abdominal pain in childhood

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SUMMARY Children aged at least 4 years admitted to hospital with acute abdominal pain, excluding appendicitis, were investigated for the presence of viruses. Out of 181 children 29 were found with viruses of whom 18 had nonspecific abdominal pain. Eight others were found to have virus-like particles on electron microscopical examination of their faeces. Virus infections contribute to a small extent to nonspecific abdominal pain in childhood, but in many cases the cause remains unknown.

In any series of children with acute attacks of abdominal pain worrying enough to require admission to hospital, there is a large proportion (30% in Jones, 1976; 36% in Sims and Alexander, 1976), in which no cause for the pain is identified. In some of the remaining cases it is possible to demonstrate the presence of a respiratory virus infection.

Kerr *et al.* (1975) looked at two epidemics of influenza B in Newcastle and found that a high proportion (41%) of those aged at least 4 years had abdominal pain as a major symptom. Children admitted to this hospital with abdominal pain in 1973 and 1974 were studied retrospectively, identifying some with positive virology (Sims and Alexander, 1976). We decided to look prospectively at admissions of children with acute attacks of abdominal pain to try to ascertain (1) which viruses could be demonstrated, and (2) whether these viruses affected particularly those with unexplained abdominal pain and fever.

Method

Children aged at least 4 years were entered into the study if they were admitted as an emergency complaining of acute abdominal pain between mid-July 1975 and the end of April 1977. Those with acute appendicitis were excluded.

On admission the children had the following investigations: (1) Nasopharyngeal secretions (NPS) for viral diagnosis by the flourescent antibody technique (FAT) and by culture. (2) Nose and throat swabs for viral culture. (3) Stool for viral culture and electron microscopy (EM). (4) Serum for viral antibody titres by complement fixation. Blood samples 10 days later were repeated if possible. (5) Blood for a white cell count and differential. (6) Urine for culture and microscopy. (7) Throat swabs for bacterial culture.

Results

During the 21½ months of the study, there were 297 admissions with acute abdominal pain and 85 (29%) of these had appendicitis. 181 (85%) of the remaining 212 had some virological screening and were studied further. Most of those who had no specimens taken were admitted and discharged over a weekend. 80 (44%) of the detailed study group were boys and 101 (56%) were girls. Their ages ranged from 4 to 16 years. 123 (68%) had had pain for 2 days or less, and only 22 (12%) had had pain for over 4 days. 37 (20%) had abdominal pain only; 84 (46%) had associated vomiting. 49 (27%) had fever ≥38°C during their admission. There was no clustering of cases or seasonal variation.

The diagnoses are listed in Table 1. Children diagnosed as having nonspecific abdominal pain had acute pain, without any apparent cause, associated sometimes with vomiting and generally lasting for 1–2 days before settling. Those diagnosed as having recurrent abdominal pain had an acute

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episode of pain with a history of a number of similar previous episodes where no cause had been found.

Investigations are listed in Table 2.

We identified 33 viruses in 29 (16%) cases, 18 of whom had nonspecific abdominal pain (Table 3). Virus-like particles were seen on electron microscopical examination in the faeces of 8 additional children. Four had spherical particles of 19–22 nm with well defined capsids and generally showing hollow forms (Fig. 1). Three had spherical particles of 28–31 nm with well defined capsids, capsomeres

Table 1 *Diagnosis made in children admitted with acute abdominal pain, excluding those with appendicitis*

Diagnosis	*Children (n = 181)*	%
Nonspecific abdominal pain	99	55
Upper respiratory tract infection	28	16
Recurrent abdominal pain	14	8
Urinary tract infection	8	4·5
Constipation	6	3·3
Mesenteric adenitis (at laparotomy)	6	3·3
Significant psychological problems	5	2·8
Gastroenteritis	5	2·8
Pneumonia (one pneumococcal)	3	
Meningitis	2	
Hepatitis	2	
Subacute intestinal obstruction; torsion of ovary; duodenal ulcer	1 each	

Table 2 *Investigations performed in 181 cases of acute abdominal pain*

Investigation	*No.*	%
Nasopharyngeal secretions	176	98
Nose and throat swabs	162	91
Stool specimen	94	53
Paired sera	109	61
White cell count	169	95
Urine examination	165	93
Throat swab (bacteriology)	144	81

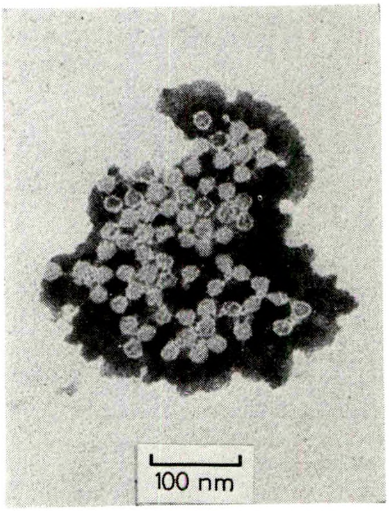

Fig. 1 *19–21 nm particles agglutinated with patient's convalescent serum.*

Table 3 *Viruses found in 181 cases of acute abdominal pain*

Clinical diagnosis	*Virus found*	*Total*	*Methods of identification*				
			FAT on NPS	*Culture of nose and throat swab*	*Culture stool*	*E/M*	*Rising antibody titre*
Nonspecific abdominal pain	Influenza A	4	1	1			4
	Influenza B	2*	1	1			1
	Parainfluenza 1	1		1			
	Mumps	1					1
	Echo 30	1		1			
	Echo 3	1			1		
	H-rhino	2		2			
	Herpesvirus	1		1			
	Coxsackie B5	2*			2		
	Coxsackie B6	1			1		
	Astrovirus	1*				1	
	Rotavirus	1				1	
	Enterovirus ?type	2**				2	
	Coronavirus	1*				1	
Upper respiratory tract symptoms	Influenza A	2	2				2
	Influenza B	2	2				
	Parainfluenza 1	1*	1				
	Coxsackie B5	1*			1		
	Enterovirus ?type	1				1	
Meningitis	Echo 30	1			1		
	Echo 19 (also found in CSF)	1		1	1		
Gastroenteritis	Echo 1	1			1		
Recurrent abdominal pain	Coxsackie B5	1			1		
Duodenal ulcer	Astrovirus	1				1	
Total		33	7	8	9	7	8

*Two viruses found in one patient.

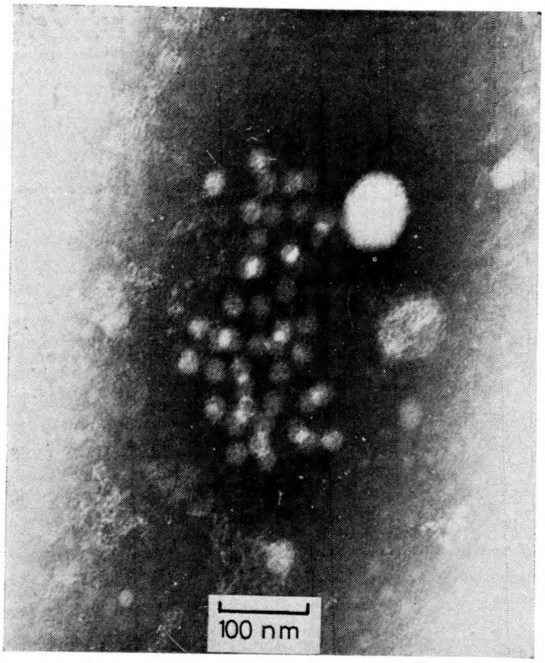

Fig. 2 *28–31 nm particles agglutinated with patient's convalescent serum.*

were very small, and hollow forms were absent (Fig. 2). In one child, both types of particles were seen; 5 of these 8 children had nonspecific pain, 2 had recurrent pain, and one had associated upper respiratory tract symptoms.

Seven (4%) of the children had a group A β-haemolytic streptococcus grown from the throat swab. Five of these had symptoms of an upper respiratory infection; one had a urinary infection; one had nonspecific abdominal pain and echo 30 in his upper respiratory tract.

31 (17%) of patients had neutrophil counts of at least $8 \cdot 0 \times 10^9/l$, and of these, 3 had urinary tract infections and 2 pneumonia. Only 8 had a lymphopenia of $1 \cdot 5 \times 10^9/l$ or less. There was no correlation between the white cell count and the presence of a virus.

A fever of 38°C or above was found in 49 (27%). Of those children with nonspecific abdominal pain, fever was found more often in those in whom a virus was present (6 of 18) than in those in whom a virus was not found (12 of 81). The numbers are small and there is no statistical significance ($P<0 \cdot 1$).

Discussion

Viral infection in childhood seems to play only a small part in the production of abdominal pain.

Viruses are found in asymptomatic children, particularly in faeces (Gamble, 1962; Galbraith, 1965), but also in the upper respiratory tract (Poole and Tobin, 1973; Horn and Yealland, 1974). The present series was not controlled because of the difficulty in obtaining appropriate controls matched for age and season. One would perhaps expect to find a virus in children with symptoms of upper respiratory tract infection, gastroenteritis, or in certain cases of meningitis. Abdominal pain associated with upper respiratory tract symptoms is often called mesenteric adenitis and presumed to be viral.

It is the group with nonspecific pain which is particularly interesting. We found a virus in 18 of 99 children with this diagnosis.

There was not a particularly large epidemic of influenza A or B during the study period or we might well have found a more striking relationship with these viruses. Kerr *et al.* (1975) noted that there had been an increase in the number of admissions with abdominal pain during the influenza B epidemics of 1973 and 1974.

An increasing number and variety of virus particles is being found in faeces by electron microscopical studies, and some unidentifiable virus-like particles were found in the faeces of the study children. Until more is known about the incidence of these particles in asymptomatic people their significance will remain in doubt.

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Current topics

The diagnosis of coeliac disease

A commentary on the current practices of members of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN)

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SUMMARY In 1977, 53 members of ESPGAN completed a questionnaire on their current practice in diagnosing coeliac disease. The usefulness of the 'Interlaken' criteria enumerated 9 years previously was reassessed. Details were obtained about the initial diagnostic approach, the acceptable histological criteria of the initial jejunal biopsy, and the timing, technique, response, and interpretation of early and late rechallenges with gluten.

Answers indicated that, although the initial mucosal lesion is usually 'flat' at the time of diagnosis, a few infants may present at a time when the mucosal lesion is less completely damaged. Furthermore, the degree of histological change after gluten challenge that is acceptable as a positive response may vary according to the state of the mucosa before challenge.

It was noted that there are still no generally agreed criteria by which the histological lesions may be described, so that (after further discussions at the Third International Coeliac Conference in Galway) a European panel has been set up to make recommendations.

In the experience of ESPGAN members, most coeliac children will have a histological relapse within 2 years of reintroduction of gluten. But a small number of unorthodox cases were reported that suggest that (a) histological relapse may take longer than 2 years to appear, or (b) the degree of sensitivity to gluten may vary at different ages.

Very long-term follow-up will be needed to explain these anomalies. Meanwhile the search continues for 'the basic defect'.

In 1969, members of the (then) European Society of Paediatric Gastroenterology discussed in Interlaken the criteria for diagnosing coeliac disease. Their conclusions were published (Meeuwisse, 1970) and contained the following points: (1) Coeliac disease is a permanent condition of gluten intolerance. (2) The initial mucosal lesion is 'flat', and recovers on a gluten-free diet. (3) Reintroduction of gluten will produce a histological relapse within 2 years.

These points were subsequently described as criteria for the definitive diagnosis of coeliac disease in childhood (Visakorpi, 1974).

It was also noted in Interlaken that transient gluten intolerance, if it exists, is rare, and that more facts are needed.

Nine years after the original discussion, 53 members of the (now) European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) completed a questionnaire on their current practice in diagnosing coeliac disease. The questions were designed to find out how often and in what manner 'the Interlaken criteria' were used.

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Details were obtained about the initial diagnostic approach to a child with suspected coeliac disease; the most commonly used laboratory tests; the acceptable histological criteria of the initial biopsy; and the timing, technique, response, and interpretation of early and late rechallenges with gluten. The results were discussed at the annual meeting in Utrecht in 1977, and some of the basic data have been presented elsewhere (Shmerling, 1978).

We believe that this questionnaire and the ESPGAN discussion that followed have given important information to test the validity and usefulness of 'the Interlaken criteria' and have raised new problems in the diagnosis of coeliac disease. We met in Zurich in September 1978 to examine further the results of the questionnaire and the discussion that took place in Utrecht. The following paragraphs are our commentary, based on the current thinking and practice of the members of ESPGAN.

Initial mucosal lesion

A 'flat' mucosa with absent or nearly absent villi has been widely accepted as an essential diagnostic feature of coeliac disease in childhood (Visakorpi, 1974). The discussions in Utrecht showed that this continues to be the usual finding in untreated childhood coeliac disease. However, it now appears certain that, in a few cases (which have been confirmed later by positive gluten challenge), the initial mucosal lesion is not 'flat' but is 'severely damaged' (Walker-Smith *et al.*, 1978). This less extreme lesion has been found in young infants and is likely to be the result of a relatively low gluten intake, ingested over a relatively short period. Great caution must be shown before diagnosing coeliac disease in such infants with less severe mucosal lesions, because there are other conditions that can cause similar histological changes. If the condition of the child permits, it may be possible to continue a diet containing a known (adequate) amount of gluten for a few weeks before repeating the biopsy. Whether or not this practice is adopted in individual cases, all must be rechallenged later (see below) for final proof of the diagnosis.

During these and subsequent discussions (at the Third International Coeliac Conference in Galway) it became clear that there are still no generally agreed criteria by which the histological lesions may be described. A European panel has been set up to make recommendations.

Gluten challenge

It is a central part of the definition of coeliac disease that the disease is permanent. The implication that follows is that reintroduction of gluten into the diet (a gluten 'challenge') will produce a relapse.

In the original Interlaken paper, it was stated that 'the only decisive criteria are the abnormal morphology of the small intestinal mucosa, its normalisation on gluten withdrawal, and the reaction on reintroduction of gluten.' It was also stated that the mucosa should be normal before rechallenge.

In 1977, the only significant change in these views related to the state of the mucosa before attempting rechallenge, and to the degree of mucosal change that is induced by the challenge. About 14% of members now consider that it is not necessary for the mucosa to be completely normal before attempting challenge; in such cases the reappearance of severe lesions would be necessary before deciding that the challenge was 'positive'. About the same proportion of members felt that, if the mucosa before challenge was normal, then a 'deterioration' of mucosal histology could be considered evidence of a positive response.

There is obvious need for caution in this approach, otherwise coeliac disease will be wrongly diagnosed and its frequency will be overestimated. A further difficulty at present is our inability to define precisely the degree of mucosal change. This is another area where it is hoped that the European panel will be able to introduce more satisfactory criteria.

Transient (temporary) gluten intolerance and 'the 2-year rule'

At Interlaken, the panel and most of the audience agreed that transient gluten intolerance (if it exists) is relatively rare. It was further stated that 'before a patient is classified as having been suffering from transient gluten intolerance the intestinal biopsy should still be normal 2 years after the reintroduction of gluten'.

In Utrecht, there was general agreement that the condition does exist, that it usually occurs in young infants, and lasts 'for a short period'—generally a few weeks or months. The pathogenesis may be similar to that in cows' milk protein intolerance. There are no firm data on the upper age limit or maximum duration of transient gluten intolerance. Stricter criteria, including a positive early challenge and a negative late challenge have been described elsewhere (McNeish *et al.*, 1976), but they are difficult to apply routinely. It should be noted that a positive early challenge will be found in both transient intolerance and coeliac disease, and that a late challenge will be required to confirm either diagnosis.

The '2-year rule' was originally developed in the context of temporary gluten intolerance (see above), but it carried the implication that, in cases of permanent gluten intolerance (that is, coeliac disease), there would be a recurrence of the mucosal lesion within 2 years of gluten reintroduction. Discussions at Utrecht confirmed that this concept had proved useful, and that most coeliac children who have been challenged have obeyed it. ESPGAN members have performed challenges on 652 children, and 619 (95%) have shown mucosal relapse within 2 years. Those who did not relapse within 2 years may represent a heterogeneous population, since the cases were studied in different centres at different ages, and with no uniformity of approach to the method of gluten challenge. They comprise at least two groups. In the first, there was no relapse after gluten reintroduction, and these children may have had transient gluten intolerance that had recovered spontaneously. In the second group, 7 members reported 20 patients in whom there was a histological relapse after 2½ to 7 years. Precise information is available on only 7 of these children, and still more thorough analysis of their data is needed and is being sought. If these claims are substantiated, they may alter recommended clinical practice.

Permanence of coeliac disease and gluten challenge

This key concept appears to have been accepted in principle. The implication that follows is that gluten challenge will always produce a relapse. While the answers to the questionnaire indicated virtual unanimity of belief on this point, there remains a considerable discrepancy in clinical practice. Some members thought that the place for gluten challenges was in research clinics only, and did not challenge their patients; others did not routinely challenge patients in whom early diagnostic features and responses to a gluten-free diet were 'classical'; still others challenged only those infants in whom the initial diagnoses were made at less than one year, in the belief that it is in this age group that there might be confusion between coeliac disease and transient gluten intolerance.

The gap that exists between theory and practice is illustrated by the fact that only 652 gluten challenges have been performed in clinics that must contain several thousand 'coeliac' children.

Conclusions and some questions for the future

The 1969 Interlaken statement concluded: 'these results do not solve the problem of diagnostic criteria of coeliac disease, and do not impart to us the "final truth" about the disease'. Nearly a decade later, the 'final truth' still eludes us, but we think that the original criteria have served us well, and at present do not need to be changed. The basic data from the 1977 questionnaire (Shmerling, 1978) indicate a considerable degree of uniformity of thinking, and the Interlaken statement has clearly been influential.

Some workers have a less rigid approach than formerly to the minimum diagnostic histological criteria of the initial biopsy. There is obvious need for caution in this approach, otherwise coeliac disease will be wrongly diagnosed and overdiagnosed. It is hoped that the European panel will be able to define the histological lesions more satisfactorily.

The need for gluten challenge is widely recognised but is less widely practised. Research workers will rightly continue to say that all coeliac patients should have confirmatory gluten challenge. But first, more satisfactory criteria for a positive challenge are needed, and this itself requires more research. For the practising clinicians who at present choose not to challenge every patient, there are no definite rules about whom they should select for challenge. Some recommend for challenge all those in whom the original diagnosis of coeliac disease was made before age one year, and those in whom the original features or therapeutic response was not 'classical'. Of course this begs the question.

When the '2-year rule' is applied, some unanswered problems arise that will only be resolved by very long-term follow-up. A positive gluten challenge is used to indicate *permanence* of the intolerance, whereas it only proves *persistence* of the abnormality. Furthermore, it is possible that clinical (and possibly histological) 'expressivity' of the disease, including the degree of gluten sensitivity, may vary at different ages. Three cases (Schmitz *et al.*, 1978) have already been reported in whom a positive gluten challenge was later followed by apparent gluten tolerance, as indicated by spontaneous remission of the small intestinal mucosal lesion on a gluten-containing diet. These cases were older and the period of gluten intolerance was much longer than cases of 'transient' intolerance.

The 7 (or more) cases in whom the mucosal lesion took longer than 2 years to relapse after gluten reintroduction require more detailed documentation. If the claims are substantiated they may alter recommended clinical practice, if not basic pathophysiological concepts.

Lastly, what should be the management of the child whose original features and histology suggest coeliac disease, who apparently recovers on a gluten-free diet, but in whom no adverse response to gluten occurs after 2 years of reintroduction? Some, perhaps the majority, will rightly be considered to have had 'transient' intolerance which is now cured, and will be discharged from the clinic. The coeliac research worker will consider all the above discussions, and may decide upon very long-term follow-up to exclude late relapses.

Meanwhile the search continues *in vitro* (Katz and Falchuk, 1978) and *in vivo* for 'the basic coeliac defect'. The answers to some of the clinical problems discussed above may have to await this dénouement.

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Change of reference style

From January 1980, the *Archives* will change its style for citing references and will follow the number system. We are making this change in order to conform with the 'Vancouver style' of uniform requirements for manuscripts submitted to biomedical journals.

Previously the *Archives* has used the Harvard reference system. Its advantages and disadvantages compared with those of the number system have seemed evenly balanced, but the editors have been aware of the burden imposed on authors and their secretaries by the different styles which different journals require. Therefore, with the unanimous agreement of the editorial committee, we have decided to support a move whereby a large—and increasing—number of major medical journals will accept manuscripts presented in one agreed style.

The system numbers references consecutively in the order in which they are first mentioned in the text. References are identified in the text by arabic numerals. For further details see instructions to authors inside the front cover, and the references cited.[1,2]

From now onwards all manuscripts submitted should accord with the new style.

[1] International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979; **1**: 533–535.

[2] Lancet. The Vancouver style. Uniform requirements for manuscripts submitted to biomedical journals. *Lancet* 1979; **1**: 429–430.

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Short reports

Caffeine secretion into breast milk

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SUMMARY Serum and milk concentrations of caffeine were measured in 5 breast-feeding mothers after a standardised oral dose of caffeine. Peak concentrations of caffeine in serum and milk were attained 60 minutes later. Binding of caffeine by constituents of serum and breast milk was low (25 and 3·2% respectively). In breast milk, caffeine binding is associated with the cream layer, and correlates with the butter fat content. Caffeine does not diffuse freely into breast milk and concentrations in milk are lower than in maternal serum.

Most breast-feeding mothers will ingest daily some quantity of caffeine from coffee, tea, or soft drinks. Information about the passage of caffeine from serum into breast milk, however, is limited (Illingworth, 1953). We studied the relationship between serum and milk concentrations of caffeine after the ingestion of a standardised oral dose.

Subjects

Five healthy white women participated in the study. The subjects ranged in ages from 25 to 31 years, weighed 53·1 to 70 kg, and had been nursing their infants for periods of 4 months to one year. The purpose and procedure of the study was explained to each woman and her informed consent obtained. Each was asked to refrain from taking any coffee, tea, or soft drinks in the 24-hour period immediately before the study.

Methods

All studies were done approximately 2 hours after a morning meal. 150 or 300 mg caffeine in the form of caffeine sodium benzoate diluted with approximately 2 oz (60 ml) water was taken by each woman within a 3-min period. Blood and milk were collected at time 0 and at 30, 60, and 120 minutes after taking the caffieine.

The caffeine concentrations in serum and breast milk were measured by gas liquid chromatography. 250 μl milk and 100 μl serum were pipetted into 12 ml conical tubes into which etidocaine, the internal standard, had previously been pipetted and dried. Samples were capped and stored at −20°C until analysis. Extraction was carried out by adding 5 ml isopropyl alcohol and chloroform (5:95) to each specimen, mixing for 30 seconds with a Vortex mixer, freezing the aqueous layer by immersion of the tube in a dry ice and acetone bath, and decanting the organic layer. The extraction was repeated, and the organic phases pooled and dried under nitrogen. Each dried extract was redissolved in 50 μl chloroform and 2 μl was injected into the gas chromatograph. A Hewlett-Packard 5830A gas chromatograph was equipped with a flame ionisation detector and a 1·8 m glass column packed with 3% SE–30 on 100–120 Gas Chrom. Q (Applied Science). The initial oven temperature of 195°C was kept for 2½ minutes and then it was increased at a rate of 2°/min. Injector temperature was 250°C, and the detector temperature 300°C. Nitrogen flow was 35 ml/min. Retention time of caffeine and etidocaine were 3·44 and 6·8 minutes respectively. Peak height ratios were calculated and compared with drug supplemented standards processed identically for determination of concentrations of caffeine in the samples of milk and serum.

Protein binding of caffeine in milk and serum was determined by equilibrium dialysis. 10 μl ^{14}C-labelled caffeine (40–60 mCi/mmol) (New England Nuclear) was added to 1 ml samples of milk and serum which then were dialysed against 1 ml 0·2 mol/l phosphate buffer, saline solution, pH 7·4 at an osmolality of 290 mmol. After incubation at 27°C for 5 hours, radioactivity was counted in duplicate aliquots of sample and dialysate. The fraction of unbound drug was calculated by dividing the radioactivity in the dialysate by the radioactivity in the sample. Binding of caffeine in skimmed breast milk and cream was studied by adding radioactive caffeine to whole milk, separating the layers by centrifugation, and performing equilibrium dialysis on both the skimmed milk and cream layers as described above. Butter fat content of the milk was determined by Pevely Dairy Company, St Louis, Missouri.

Results

The Table summarises the data obtained from the 5 women. After the ingestion of 150 mg caffeine, peak concentrations of caffeine in serum ranged from 2·39 to 4·05 μg/ml, and peak concentrations in milk ranged from 1·4 to 2·4 μg/ml by 60 minutes. Doubling the dose of caffeine to 300 mg resulted in a doubling of the serum caffeine concentration at 30 and 60 minutes and did not alter the milk to serum concentration ratio in the one woman studied. At all time intervals the caffeine concentration in milk correlated with that in serum ($0 \geq 30$ min, $r = 0{\cdot}93$; $30 \geq 60$ min, $r = 0{\cdot}80$; $60 \geq 120$ min, $r = 0{\cdot}90$). For each time interval, the correlation coefficient (r) between the concentrations in serum and milk was 0·89. Analysis by linear regression indicated a linear relationship between serum (x) and milk (y) caffeine concentrations with an intercept (b) of 0·342 and slope (a) of 0·381 ($y = ax + b$).

Caffeine appeared to equilibrate rapidly between serum and breast milk. No caffeine was detected in baseline samples of milk or serum. The average of the milk to serum concentration ratios was 0·52 (SD 0·098). The ratios were derived from comparisons of the areas under the paired concentration versus time curves (milk divided by serum) and provide a measure of average concentration ratios over time. The one-way analysis of variance was used to test the possibility that the milk to serum concentration ratio varied significantly at each time interval. No significant differences were found ($F = 0{\cdot}972$; $v_1 = 2, v_2 = 12$).

The average binding of caffeine to constituents of serum and whole breast milk was 25·1% (SD 2·97) and 3·2% (SD 2·04) respectively. After centrifugation of the breast milk, all of the binding was accounted for by the creamy layer, no binding being detected in the skimmed breast milk. The butter fat content of the milk correlated with caffeine binding ($r = 0{\cdot}62$). Analysis of the relationship of the fat content of milk (x) to the percentage of caffeine bound in milk (y) by linear regression indicated an intercept (b) of 0·22 and a slope (a) of 1·47. The fat content of the five samples ranged from 1·8 to 6·1%. An average of 4·2% (SD 2·4) of the caffeine in cream was nondialysable, a percentage which agrees well with the 3·2% binding determined in whole breast milk.

Discussion

After the newborn period, nursing infants are likely to ingest caffeine in breast milk. Caffeine, a methyl xanthine present in coffee, tea, and soft drinks (Abramowicz, 1977), is a neurological and myocardial stimulant and may cause coronary artery dilatation, smooth muscle relaxation, skeletal muscle contraction, or diuresis (Ritchie, 1975).

The administration of 2·5 to 5 mg/kg caffeine to preterm infants once or twice daily after a loading dose of 10 mg/kg produces a significant decrease in apnoeic spells (Aranda *et al.*, 1977). There is little information however, about other specific effects, or about the toxicity of caffeine in infants. One 12-month-old child who took between 1 and 1·5 g developed agitation, hyperglycaemia, hypertension, tachycardia, haematemesis, and diuresis (Sullivan, 1977).

Table *Caffeine concentrations in serum and breast milk after an oral dose of 150 mg*

Subject	*Serum concentration (μg/ml)*				*Milk concentration (μg/ml)*			
	0 min	*30 min*	*60 min*	*120 min*	*0 min*	*30 min*	*60 min*	*120 min*
1	ND	1·6	2·4	1·4	ND	1·11	1·43	1·1
2	ND	3·2	2·9	1·6	ND	1·73	1·25	0·54
3	ND	4·0	4·0	1·9	ND	2·29	2·41	1·16
4	ND	2·9	3·1	2·3	ND	1·4	1·3	1·02
5	ND	3·5	3·2	1·9	ND	1·4	1·08	0·81
$\overline{X}$		3·05	3·1	1·6		1·58	1·49	0·926
SD		0·925	0·605	0·536		0·451	0·527	0·253
5a*	1·0	5·8	6·5	4·6 (150 min)	ND	2·8	2·5	2·1

ND = Not detectable. *Caffeine dose, 300 mg.

Newborn infants eliminate caffeine more slowly than adults and could develop high concentrations if comparable amounts were taken regularly. The half-life of transplacentally acquired caffeine in term newborn babies averaged 80 hours (Parsons *et al.*, 1976) (SD 26 hours). For preterm infants, caffeine elimination is even slower; an average half-life of 97·5 hours was reported in one study (Aranda *et al.*, 1977). Both of these values for half-life are much longer than the average of 3·5 hours reported for adults (Parsons *et al.*, 1976). The average half-life of caffeine for infants after the newborn period is unknown. If caffeine intake was sizeable and if caffeine half-life was comparable with the values found for newborn infants, toxic concentrations might accumulate in infants of nursing mothers with large caffeine intakes.

Our studies show that although caffeine rapidly enters breast milk, the concentrations in milk are less than expected at equilibrium after diffusion. If caffeine diffused freely from serum to milk, caffeine binding to milk and serum constituents should determine the distribution ratio. Considering that 75% of serum caffeine was unbound and available for diffusion into milk, the predicted milk to serum concentration ratio is 0·78*. The lower ratio (0·52) we observed could indicate either that the caffeine-equilibrated milk was diluted by one-third with milk secreted before caffeine dosage, or that some additional barrier reduces the diffusion of caffeine into milk. If the former were true, at later times the ratio of caffeine concentrations in milk versus serum should have increased as the dilution effect was reduced. We tested this possibility, and the differences in the average ratios at different times were insignificant, indicating no evidence of dilution. We conclude that the data indicate that the diffusion of caffeine from serum into milk is influenced by factors other than the degree of protein binding.

The property of reduced binding of caffeine by constituents of milk relative to those in serum may be an additional factor influencing drug concentration in milk. Decreased binding in milk relative to serum has been demonstrated for the related methyl xanthines, theophylline (Yurchak and Jusko, 1976), and theobromine (Resman *et al.*, 1977). This would tend to reduce the chances of an infant ingesting toxic amounts of these and other drugs that behave in a similar manner.

Can an infant acquire a significant concentration of caffeine by nursing? Our studies indicate that the nursing infant would receive only a low dose of caffeine after the mother drank a single cup of coffee (150 mg caffeine). A litre of breast milk collected during the first hour after the mother's dose would contain approximately 1·5 mg caffeine. With repeated maternal caffeine ingestion, the caffeine accumulated in the infant would depend on the average concentration in maternal serum and breast milk over time, the volume of milk ingested, and particularly, the infant's clearance rate for caffeine. If older infants have prolonged caffeine elimination rates comparable with newborns, they might accumulate significant amounts of caffeine, although the concentration of caffeine in breast milk is relatively low. Additional studies among infants nursing from mothers who routinely ingest more caffeine than we gave, and studies of caffeine clearance in older infants, are necessary to answer the question.

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*If the unbound fractions diffuse freely and are in equilibrium, and if the concentration in serum is unity, the expected ratio of concentrations in milk versus serum is calculated (0·75 (unbound in milk) + 0·03 (bound in milk) ÷ 0·75 (unbound in serum) + 0·25 (bound in serum)) = 0·78.

Recurrent osteolytic lesions and subcutaneous fat necrosis in association with a developmental pancreatic cyst

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SUMMARY A girl had repeated episodes of widespread osteolysis, subcutaneous fat necrosis, and periarticular fat necrosis mimicking arthritis. Her symptoms persisted for 4 years, after an initial episode of severe abdominal pain, and were accompanied by only minor abdominal symptoms. She was found to have a developmental pancreatic cyst (which was excised).

Disseminated fat necrosis is a rare complication of acute or chronic pancreatitis and pancreatic pseudocysts. It is usually an isolated rather than a recurrent event. This report describes a child with repeated osteolytic lesions, occurring over a 4-year period, in whom the diagnosis was ultimately made of a developmental pancreatic cyst.

Case report

A 7-year-old English girl was referred to this hospital in January 1977 with painful swollen fingers and toes. She had presented elsewhere shortly before her 5th birthday with swelling of the dorsum of the right foot. This had settled on antibiotics after drainage of a large amount of pus, but no organism had been isolated. One week later she had developed severe abdominal pain and fever, and at laparotomy free pus was present. This had again been sterile and no cause was found. A diagnosis of primary peritonitis had been made, antibiotics were continued, and she made a complete recovery.

After a further 3 months she had developed painful swelling of the dorsum of the left hand and of 2 toes on the left foot, with intermittent pyrexia. WBC was 22×10^9/l, predominantly neutrophils but with an eosinophilia of $1\cdot7 \times 10^9$/l. Antibiotics had been given and the lesions resolved. Three weeks later she had developed a painless, hot swelling of the thigh which became fluctuant. 1 ml of sterile fluid was aspirated. Immune deficiency was suspected but full investigations did not support this.

One year later, after a bout of diarrhoea, she had further pain and swelling of 2 toes and the terminal phalanges of all fingers of the right hand, and was referred to this hospital. On direct questioning it was found that all previous episodes had been accompanied by loose stools and she had had occasional bouts of abdominal pain, although these were not sufficiently severe for her to see a doctor.

X-rays of the affected areas showed lytic lesions breaching the cortex but without periostitis. The differential diagnosis initially was felt to be between leukaemia, sickle cell disease, histiocytosis X, multiple septic emboli, and other causes of osteolysis. Blood film showed no anaemia, no leucocytosis, and no abnormal cells, but slight eosinophilia. Haemoglobin electrophoresis was normal, as were neutrophil function tests. Antibiotics were withheld and the pain and swelling settled over a few weeks, with considerable recalcification radiologically (Fig. 1).

The girl remained well for a year, during which time she failed to attend follow-up appointments. She then presented, again after a bout of diarrhoea, with swelling of the hands and feet settling without

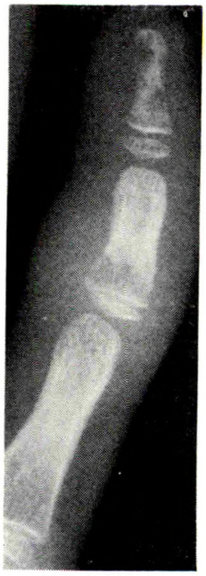

Fig. 1 *Osteolytic lesions of the 5th finger January 1977. (12 months later x-ray showed disappearance of the lesions).*

treatment. Two weeks later she was admitted with swelling of one of the labia majora and subsequent panniculitis of the adjoining part of the thigh. A mass palpable in the left hypochondrium was thought to be the spleen. However barium meal showed a soft tissue mass in the region of the left kidney. Intravenous pyelogram and anterior ultrasound examination were both normal, but a CAT scan showed a cyst near the tail of the pancreas (Fig. 2). Serum amylase was >2000 Somogyi units/100 ml (normal <200 units/100 ml). There was no history of abdominal trauma nor was there any suspicion of non-accidental injury.

At laparotomy the pancreas appeared normal. A 6 cm cyst lay between the colon and the pancreas but separate from both. This was excised. Histology showed a cyst made of a fibrous wall, lined by mucous columnar cells. Within the wall were glands lined by mucous columnar cells, goblet cells, columnar cells with a brush border, and Paneth's cells. In addition, the wall contained pancreatic acini and islets of Langerhans. The appearances were of a pancreatic developmental cyst incorporating both intestinal and pancreatic tissue. Subsequently the patient has remained symptom-free.

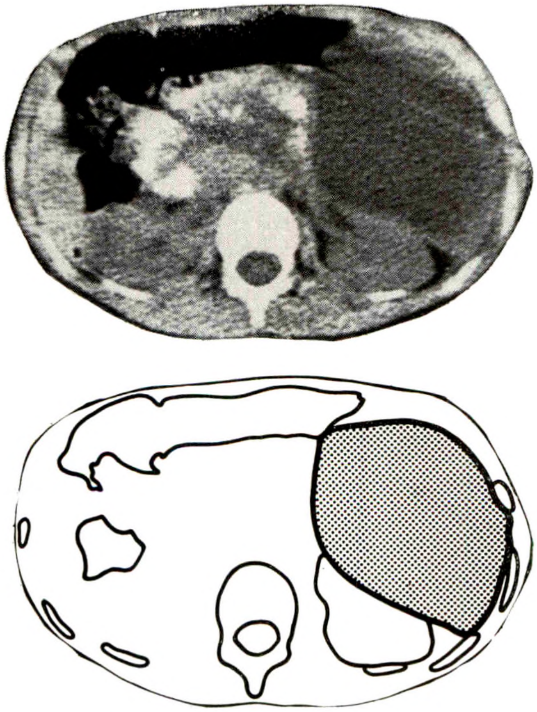

Fig. 2 *CAT scan of the abdomen. Position and extent of cyst are shown in diagram.*

Discussion

Although fat necrosis associated with pancreatic disease is usually intra-abdominal, disseminated fat necrosis may occur in the subcutaneous, periarticular, bone marrow or visceral fat. This is caused by pancreatic enzymes released into the circulation, and osteolysis may be secondary to necrosis of bone marrow or due to damage of small vessels by lipase (Achord and Gerle, 1966). Osteolytic lesions may be multiple and silent, but tend to be painful when affecting the small bones of the hands and feet. In children *x*-rays show punched-out lesions, sometimes with breach of the cortex and overlying periostitis, and radiological resolution may take months. The lesions are similar to the osteolytic lesions of metastatic neoplastic disease, sickle cell disease, and haematogenous osteomyelitis.

Subcutaneous fat necrosis presents as tender nodules while necrosis of periarticular fat may mimic arthritis. Fever, leucocytosis, and eosinophilia are common. Disseminated fat necrosis is a recognised complication of acute or chronic pancreatitis and pancreatic pseudocysts. When following acute pancreatitis the lesions may appear some weeks after apparent recovery (Shackleford, 1977).

Pancreatitis in childhood is being recognised with increasing frequency. Trauma is the most common cause, particularly handlebar injury, but child abuse should be excluded. Drugs, particularly corticosteroids and thiazide diuretics, may be responsible, and pancreatitis may be associated with mumps in which case it is invariably slight.

Pancreatic pseudocysts can follow acute pancreatitis and in most cases trauma has been implicated or suspected (Moossa, 1974). The child commonly presents some days or weeks after the injury with repeated vomiting or an 'acute abdomen'. A true cyst of the pancreas is said to be histologically distinguishable from a pseudocyst by the presence of an epithelial lining, but in practice the distinction is often difficult. True cysts are much less common than pseudocysts and may be neoplastic, hydatid, or congenital. Congenital cysts may be associated with mucoviscidosis or polycystic kidneys, or they may be developmental. The last are exceedingly rare (Miles, 1959), the few reported cases have presented with abdominal pain or swelling. In the case reported here the relationship between the patient's abdominal pain and her symptoms from disseminated fat necrosis was obscure. Measurement of serum amylase might have enabled the diagnosis to have been made earlier.

We thank Lord Smith of Marlow, Dr S. M. Tucker, and Dr B. M. Ansell for permission to report this patient.

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Lumbar punctures, meningitis, and persisting pleocytosis

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SUMMARY A retrospective survey of children with haemophilus and pneumococcal meningitis was carried out to assess the significance of persistent CSF pleocytosis and the need for repeat lumbar punctures after adequate treatment. Persistent pleocytosis was noted in 9 of 27 patients with haemophilus meningitis; this tended to be present in those with higher initial CSF white blood counts and lower initial CSF glucose contents. No sequelae were noted in those with persistent pleocytosis. Repeat lumbar punctures were not of clinical benefit and tended to result in longer treatment which was not warranted.

One criterion used to decide when to stop treatment in a child with bacterial meningitis is the presence of a CSF white blood count of $<0{\cdot}050 \times 10^9$/l after 10–14 days of treatment (Smith *et al.*, 1973). However, not only may a lumbar puncture be dangerous (Shinefield, 1975), but children who have received apparently adequate treatment can show persistent increases in the CSF white blood count. This survey was carried out to assess the significance of persistent pleocytosis and the need for a repeat lumbar puncture in a clinically well child after reasonable treatment.

Patients and methods

Records of all patients aged over 2 months admitted to this hospital between January 1972 and July 1977 with a diagnosis of bacterial meningitis were examined. The survey was confined to those who grew *Haemophilus influenzae* or *Streptococcus pneumoniae* from their CSF. Patients with recognised anatomical defects of skull or spine, those with immunological disorders, and those who did not have lumbar punctures repeated between days 10 and 14 were excluded. Those with meningococcal meningitis were also excluded as very few have persistent pleocytosis and their prognosis is better.

All those with *H. influenzae* received chloramphenicol for at least 10 days. In addition 22 received ampicillin for 10 days. 13 were given sulphonamide and 5 were given penicillin for varying periods. All with pneumococcal meningitis received penicillin for at least 10 days. In addition, 6 were given chloramphenicol, 6 were given sulphonamide, and 4 were given ampicillin for varying periods. Persistent pleocytosis was defined as a CSF white blood count $>0{\cdot}050 \times 10^9$/l between days 10 and 14.

37 babies fulfilling these criteria were examined with regard to organism, initial and repeat CSF findings, duration of pyrexia, and sequelae. The duration of follow-up was from 1½ to 5½ years. Full physical and neurological examination and clinical assessment of hearing were carried out when the patients were recalled.

Results

Of the 37 patients studied, *H. influenzae* was isolated from 27, and *S. pneumoniae* from 10. Nine of the 37 had persistent pleocytosis and all of these grew *H. influenzae*. The initial CSF white blood counts in those with persistent pleocytosis tended to be higher if one excludes one baby with pneumococcal meningitis whose initial count was $64{\cdot}0 \times 10^9$/l (Table). This patient's CSF cell count fell to

Table *Comparison between patients with and without pleocytosis*

	With pleocytosis	*Without pleocytosis*
Number	9	28
Initial CSF WBC $\times 10^9$/l	5·79	3·402*
CSF cells $>5{\cdot}0 \times 10^9$/l at diagnosis	7	7
Temperature >37·5°C at day 5	5	3
Sequelae	0/8	4/19

*One patient with CSF WBC of $64{\cdot}0 \times 10^9$/l is excluded.

$0 \cdot 024 \times 10^9$/l on day 11, and no sequelae were noted. The initial counts between those with and those without pleocytosis overlapped. The initial mean CSF glucose content was appreciably lower in the pleocytosis group (0·3 compared with 1·9 mmol/l; 5·4 compared with 34 mg/100 ml), but again the two groups overlapped. The initial CSF protein content was similar in the two groups.

Patients with persistent pleocytosis had more lumbar punctures performed (5 compared with 1), were given antibiotics for a longer period (22 compared with 15 days), and spent longer in hospital (32 compared with 17 days), than those without pleocytosis. This prolonged time in hospital was due only to the abnormal CSF cell content. Temperatures were over 37·5°C after 5 days of treatment in 5 of the 9 babies with persistent pleocytosis, but in only 3 of the 27 without such pleocytosis. Apart from persistent pyrexia, however, the clinical course was similar in the two groups. Relapse did not occur in any of the 37 babies. Eight of the 9 with pleocytosis were re-examined after 1½ to 5½ years. None had a residual neurological deficit or a clinically significant hearing loss. 19 of the 27 without persistent pleocytosis were seen after 1½ to 4½ years. Four of these 19 had long-term complications. One girl who had many convulsions during her meningitis has moderate mental handicap and a left hemiparesis. One has mild mental handicap. One has severe unilateral deafness. The 4th had ataxia which disappeared after 3 years. Whether this was cerebellar or vestibular in origin is not known.

Discussion

In two recent reports attention was drawn to the occurrence of persistent CSF abnormalities after apparently adequate treatment of meningitis (Chartrand and Cho, 1976; Jacob and Kaplan, 1977). One-third of the patients with haemophilus meningitis in this survey had CSF white blood counts $>0 \cdot 050 \times 10^9$/l after adequate treatment. This pleocytosis was not associated with a longer clinical illness or with more complications. Nor did it presage a higher incidence of sequelae. It was related to the initial CSF white blood count and glucose content.

The CSF white blood count at diagnosis is not related to the CSF bacterial content (Feldman, 1976). It is, however, an indicator of the patient's response to infection. Also, the CSF glucose level in meningitis is related to brain metabolism and the degree of meningeal inflammation rather than to the CSF bacterial content (Menkes, 1969). Thus, persistent pleocytosis may indicate a better inflammatory response by the patient.

In the series of haemophilus and pneumococcal meningitis reported by Chartrand and Cho (1976), sequelae were present in one of 13 patients with persistent pleocytosis, whereas they were found in 3 of 15 patients without such pleocytosis. This tendency to fewer sequelae if persistent pleocytosis is present is also shown in the present survey. Thus, persistent pleocytosis may be a good prognostic finding. A recent report (Lindberg *et al.*, 1977) had suggested that chloramphenicol with ampicillin may result in more sequelae. Of 22 patients with haemophilus meningitis treated with both antibiotics in this series, none had sequelae.

When clinically indicated, a lumbar puncture is mandatory. Even if it is clear a second lumbar puncture may be indicated within a few hours (Rapkin, 1974). Repeat lumbar punctures may also be warranted at any stage during treatment if indicated by the clinical condition. However, a lumbar puncture after 10 to 14 days in this series did not contribute any useful information from the patients' point of view; for instance, no case of relapse or failure to sterilise the CSF was found. On the contrary, it tended to result in longer treatment and more time spent in hospital. A lumbar puncture may also be hazardous. Thus, in a clinically well child who has received 10 days of appropriate antibiotic treatment, routine performance of a lumbar puncture is not justified.

I wish to thank Dr P. Deasy for his helpful advice and Mrs A. McAlinden for her patience.

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Confirmation of gestational age by external physical characteristics (total maturity score)

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SUMMARY The use of the total maturity score (TMS) as a means of estimating gestational age was assessed in a population of 76 low birthweight infants (≤2500 g) and 80 matched controls (>2500 g) all of certain gestational ages. The gestational ages, derived from the last menstrual period and from the TMS, were similar except in preterm low birthweight infants. The discrepancy in this group was attributed to the structure of the scoring system. It is concluded that the TMS is a convenient and accurate method of assessing gestational age in term babies.

Considerable research has recently been devoted to evolving methods of corroborating gestational age as calculated from the date of the last menstrual period (LMP). These range from the use of ultrasound, *x*-rays, and amniotic fluid estimations during pregnancy, to biochemical and clinical procedures in the newborn. The last method can be divided into three main groups—biochemical, anthropometric, and nonanthropometric. The most widely used are external physical characteristics (Farr *et al.*, 1966), neurological signs (Robinson, 1966), or both (Dubowitz *et al.*, 1970).

The purpose of the study reported in this paper was to assess the use of the total maturity score (TMS) (Farr *et al.*, 1966) in a total low birthweight (LBW) population as a means of estimating gestational age as derived from the date of the LMP. Particular attention was paid to its accuracy in preterm LBW infants.

Method

The infants studied were a sample from a larger survey of low birthweight babies (Cater, 1978) and comprised LBW infants ≤2500 g and their matched controls of normal birthweights (>2500 g). All were of certain gestational ages and each infant was examined by J.I.C. It was fundamental to the study that J.I.C. should not know the length of gestation as stated by the mother and that the maternal history be assessed by an obstetrician, thus ensuring an independent decision concerning the accuracy of the maternal data.

The method recommends that the baby should be examined between 12 and 36 hours of age. The mean age for examination of the controls was 22·1 ± 7·6 hours; total LBW 23·2 ± 13·1 hours; LBW 24·8 ± 17·6 hours; and term LBW 21·7 ± 7·0 hours. There was no significant difference between the mean age at examination of preterm LBW infants and controls. The preterm infants were examined at a later age because of the higher incidence of illness in them.

Results

The data are presented and analysed in broad categories of controls and total LBW, with more detailed subdivision into preterm LBW and term LBW to reveal any weakness of the method. In other studies the results have been combined and presented for a single group, thus concealing the difficulties posed by the preterm subgroup.

The gestational age was derived from both the LMP and the TMS and the difference between the two methods was compared (Table). The only significant difference was found in the preterm LBW group in which the mean gestational age derived from the LMP, 32·9 weeks SD 2·9, differed from that derived from the TMS, 34·4 weeks SD 3·0 ($P < 0{\cdot}05$), a difference of 1·5 weeks. Comparison of the mean gestational ages derived from the LMP and TMS for the other three groups showed no statistical differences. The wide SD found in the total LBW group reflects the influence of the preterm LBW group.

Table *Comparison of the mean gestational ages in weeks calculated from the last menstrual period (LMP) and from the total maturity scores (TMS) in babies whose mothers were certain of their dates*

	Controls (n = 80)		*Total LBW (n = 76)*		*Preterm LBW (n = 36)*		*Term LBW (n = 40)*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Gestational age								
Derived from LMP	40·1	1·0	36·1	3·2	32·9*	2·6	39·0	1·1
Derived from TMS	40·4	1·0	36·6	3·2	34·4*	3·0	38·6	1·8

*P<0·05.

Discussion

External physical characteristics as a means of assessing gestational age were preferred to neurological signs for two reasons. Firstly, the sample was biased towards LBW, and therefore many infants would be attached to intensive care equipment, making impossible a number of tests needed for the neurological examination; secondly, it was felt that neurological signs might be altered by the delivery process and drugs given to the mother.

A number of methodological problems are evident in earlier studies. Prior knowledge of maternal dates has been a serious difficulty in several, where the investigator has both examined the baby and questioned the mother concerning the details of the LMP. Such a dual role inevitably influences the findings: the maternal menstrual data must be assessed by an independent worker.

The use of a correlation coefficient has been common in previous studies but has not been entirely satisfactory due to the paucity of babies of shorter gestations. In the present sample a relatively large number of preterm babies of known gestational ages (36/156) was included. For this reason the sample was subdivided into preterm and term LBW groups and analysed separately. The analysis highlights the technical problems of the score. It has not always been appreciated by previous investigators that the precision of the TMS varies with gestational age, since 0·9 points represents a week before 30 weeks and 0·8 points equals a week before 32 weeks, whereas at 39 weeks, 3 points represent a week. The difference in the mean gestational age for preterm infants calculated by the TMS method from that derived from the LMP is 1·5 weeks, compared with 0·4 weeks for infants at term, which shows the inaccuracy of the use of this score in the preterm LBW group

The use of external characteristics seems an easy and satisfactory method of assessing the gestational age of the term baby, and the error is well within the range acceptable in other analyses using complex biological investigations. The results for term infants are remarkably consistent, considering the vagaries of maternal memory and the tacit assumption that ovulation occurs on the 14th day of each cycle. In contrast, the results obtained for preterm infants underline the inaccuracies and uncertainty present in methods currently available for corroborating the maternal data in this group. The small numbers of infants, the effects of illness and drugs, type of delivery, and the structure of the score all militate against accurate assessment in these infants, and further study of this problem is needed.

Conclusion

For routine clinical purposes the use of the external physical characteristics is a simple and convenient method for estimating gestational age. It is particularly accurate at term but is less precise for babies of short gestation.

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Dissolution of bilateral staghorn cystine renal calculi

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SUMMARY Bilateral staghorn renal calculi in a 7-year-old girl with cystinuria were dissolved over a period of 6 months, using a high fluid intake, urinary alkalinisation, and D-penicillamine. Even in children with extensive cystine urolithiasis, medical management may avert the need for surgery.

Cystinuria is an inherited complex autosomal recessive defect in which there is decreased proximal renal tubular reabsorption of filtered cystine, lysine, arginine, and ornithine. Defective transport of these amino-acids in the gut has also been demonstrated, but the clinical symptoms are related only to the associated stone formation (Crawhall and Watts, 1968). Cystine is the least soluble of all the naturally occurring amino-acids, and crystalluria and stone formation tend to occur when the cystine concentration exceeds the solubility limit of approximately 400 mg/l (±1660 μmol/l) at pH 7·0 and temperature 37°C (Macdonald and Fellers, 1968).

The excretion of cystine in quantities large enough to cause stone formation probably only occurs in homozygotes (incidence ±1:40 000) (Dahlberg *et al.*, 1977). The age of presentation and severity of disease appear to be related more to drinking habits and other factors affecting urinary concentration than to the actual quantity of cystine excreted or the genotypic variants of cystinuria.

We report what we believe to be the first case in which bilateral staghorn cystine calculi in a child were completely dissolved by medical means.

Case report

A 7-year-old girl of mixed ethnic origin presented with recurrent urinary tract infection and haematuria. No member of her family was known to have calculi or other renal problems, but there was an unconfirmed report that the patient had once passed a small stone per urethram. Clinical examination showed no abnormalities. Her urine contained numerous pus cells and red cells, and gave a pure growth of *Escherichia coli*.

A plain *x*-ray showed the presence of bilateral renal staghorn calculi, with clusters of smaller stones in the calyces (Fig. 1). An intravenous urogram showed mild bilateral caliectasis without evidence of obstruction or renal parenchymal damage.

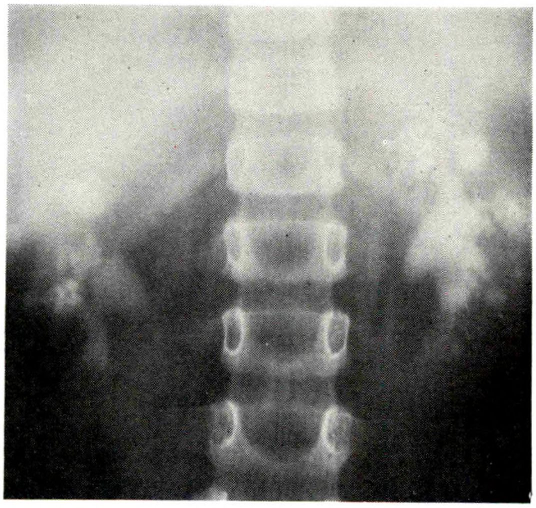

Fig. 1 *Renal tomogram before treatment showing bilateral staghorn calculi and multiple clusters of smaller calculi.*

Serum sodium, potassium, urea, creatinine, calcium, phosphorus, alkaline phosphatase, protein, uric acid, and acid-base values were normal, as were urinary pH and calcium, phosphate, and uric acid excretion values. 24-hour creatinine clearance was 110 ml/min per 1·73 m^2.

Hexagonal crystals typical of cystine were readily demonstrable on microscopical examination of a chilled early morning urine specimen which had been acidified with glacial acetic acid to pH 4. The presence of cystine in the urine was demonstrated by the cyanide-nitroprusside test. High voltage paper electrophoresis confirmed the presence of cystine, and showed abnormally large amounts of the 3 dibasic amino-acids—lysine, arginine, and ornithine. Quantitative amino-acid analysis by ion-exchange column chromatography showed that the patient was excreting >10 times the normal maximum quantity of cystine in the urine—860 μmol per 24 hours compared with the normal adult rate of <80 μmol per 24 hours. The lysine, arginine, and ornithine levels were similarly raised, confirming the diagnosis of homozygous cystinuria.

Cystine excretion by both parents and 2 of the patient's 3 siblings was moderately raised (170–340 μmol cystine per 24 hours). Levels of lysine, arginine, and ornithine excretion were also slightly raised in the father and 2 siblings, but none had radiographical evidence of renal calculi. They are therefore presumed to be heterozygotes.

Treatment and progress

The urinary tract infection was cleared with co-trimoxazole, and prophylactic chemotherapy with nalidixic acid was maintained.

Treatment was directed towards decreasing the concentration and increasing the solubility of cystine in the urine. This was achieved in three ways. Firstly, an increased fluid intake during day and night was encouraged. This effectively doubled the urine output and thus reduced the concentration of urinary cystine. Secondly, by increasing urinary pH from 6 to >7·5 the solubility of cystine was increased approximately 2-fold. 8 g effervescent sodium citrotartrate was given 4 times a day with the additional fluids and was found to be effective in keeping the urine alkaline. The added sodium load (about 200 mmol/24 hours) produced no evidence of fluid overload and had a secondary beneficial effect by inducing an osmotic diuresis. Acetazolamide and sodium bicarbonate were ineffective in keeping the urine alkaline for any length of time. Thirdly, D-penicillamine was given. This drug when excreted in the urine combines with cystine, forming the much more soluble penicillamine-cysteine complexes. The initial dose was 125 mg twice a day and during 3 weeks this was increased to 250 mg three-times daily.

Once the child had been stabilised on this regimen, she was discharged and seen monthly. She remained asymptomatic and no side effects of D-penicillamine or other treatment were observed. Patient (and parent) compliance was excellent as reflected by the passage of large volumes (1800–2300 ml/24 hours) of dilute urine, with a pH never dropping below 7·5.

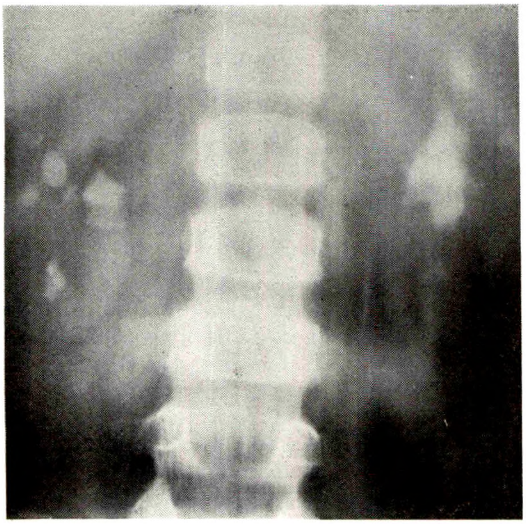

Fig. 2 *Renal tomogram after 2 months' treatment, showing reduction in size and number of calculi.*

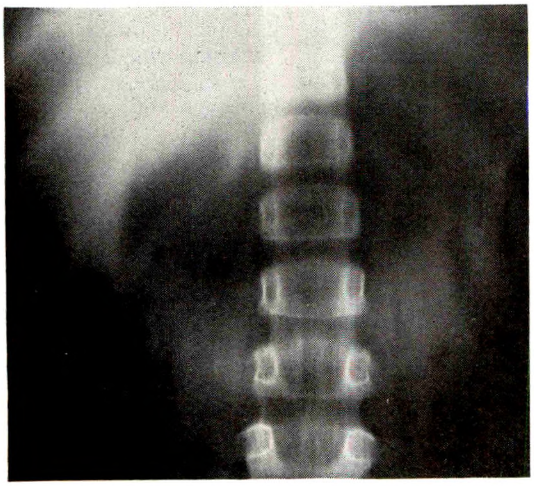

Fig. 3 *Renal tomogram after 6 months' treatment, showing no evidence of calculi.*

Within 3 months of starting treatment the renal calculi were markedly reduced in size and number, and after 6 months these had completely disappeared (Figs 2 and 3). D-penicillamine was then stopped because of the risk of long-term side effects.

Discussion

Nephrolithotomy was initially considered the prime form of treatment. The infection however was readily controlled and as no evidence of obstruction was found, and renal function was normal, immediate surgery did not seem indicated. In addition, the small but definite risk attendant on bilateral nephrolithotomy, and the fact that total removal of multiple calculi is difficult, as well as the inevitability of scarring of both kidneys which would form a nidus for further calculus formation, led us to attempt to dissolve the calculi.

Failure to dissolve calculi may be due to inadequate treatment or to lack of patient compliance: considerable motivation is required to get a child to take extra fluids, especially in the middle of the night. Calculi may also fail to dissolve either because they are mixed stones containing calcium salts due to coexisting metabolic disorders, such as hyperparathyroidism, or because of obstruction to urine flow.

Although medical management is preferable to surgery, it must be remembered that D-penicillamine toxicity is often a limiting factor (Stokes *et al.*, 1968). An acute hypersensitivity reaction with a transient rash, fever, arthralgia, and lymphadenopathy is common but will often resolve if treatment is temporarily reduced or stopped. More serious complications—such as agranulocytosis, immune-complex-induced nephrotic syndrome, drug-induced systemic lupus erythematosus, or Goodpasture's syndrome—usually require discontinuation of the penicillamine. Potential pyridoxine deficiency may be avoided by prophylactic pyridoxine therapy.

To prevent recurrence of cystine calculi, patients will need to understand that high fluid intake especially at night, and probably also alkalinisation of the urine, will have to be continued for life. D-penicillamine is best given only if new calculi are formed (Dahlberg *et al.*, 1977). Less toxic but effective agents, such as N-acetyl penicillamine (Stokes *et al.*, 1968) or mercaptopropyonylglycine (Terhorst and Stuhlsatz, 1975), may become generally available in the near future.

We thank Dr H. Henderson and Dr E. Diamond for amino-acid determinations.

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Takayasu's arteritis as a differential diagnosis of systemic juvenile chronic arthritis

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SUMMARY After a series of throat infections an 8-year-old girl presented with fever and limb pain, initially diagnosed as juvenile chronic arthritis. Persistent symptoms led to further investigations when she was shown to have an arteritis affecting her aorta.

As there are no specific diagnostic tests for juvenile chronic arthritis (JCA), a remittent fever with a high swinging pattern associated with limb pain which continues for at least 2 weeks tends to be regarded as systemic JCA. However, a number of conditions, including various types of arteritis, can also produce these symptoms (McEnery, 1977).

Case report

An 8-year-old Yugoslavian girl was referred for advice on further management of what was thought to be systemic JCA of 18 months' duration. She was the only child of healthy unrelated parents and had been well until age 7 when, during a 4-month period, she had four episodes of pyrexia to 38°C associated with pharyngitis, which were treated with ampicillin. She subsequently developed fever with a temperature which characteristically reached 40°C daily between the afternoon and midnight, and then subsided spontaneously. She was generally unwell with considerable pain in her lower limbs, but no other signs or symptoms. Initial investigations showed ESR 97 mm in 1st hour, Hb 9·9 g/dl, WBC $13 \cdot 0 \times 10^9$/l, a hypercellular bone marrow, and ASO titre <1/200; blood cultures and all other investigations were negative. Skin and muscle biopsies were normal. She was given a 10-day course of lincomycin and gentamicin but her fever persisted; there was transient improvement with salicylate. Prednisolone was started at an initial dosage of 80 mg daily with pronounced improvement in ESR and fever. Both these parameters deteriorated when prednisolone was reduced to 10 mg daily. She was continued on 10 mg prednisolone daily and aspirin until referred here one year later.

When seen she still had an occasional fever, despite the prednisolone and aspirin. She was markedly cushingoid, and was on the 50th centile for height and the 90th centile for weight. There were no specific complaints but on direct questioning she did admit to some lower abdominal pain, discomfort in the calf muscles, and bleeding haemorrhoids. There were 4 small café-au-lait spots but no other cutaneous lesions. There was no lymphadenopathy, rash, hepatosplenomegaly, or arthritis. Her pulses were easily palpable in the arms and carotids, but no pulses were felt in the femoral arteries or in the legs, which were cold and hairless. No bruit was heard. Blood pressure was 130/80 mmHg in the arms and, by Doppler, 90/0 mmHg in the legs. All other systems were normal apart from first-degree haemorrhoids. Some days after examination it became obvious that the pain in the calves was, in fact, intermittent claudication as it appeared to be closely associated with the child walking some 300–400 metres.

Investigations

ESR was raised at 57 rising to 88 mm in 1st hour on reduction of prednisolone, Hb 12·2 g/dl, WBC

12·3 × 10⁹/l—61% neutrophils, 32% lymphocytes, 6% monocytes, 1% eosinophils; IgA 4·4 g/l (normal 0·5–2·3 g/l), IgM 2·6 g/l (normal 0·5–2·0 g/l), IgG 10·4 g/l (normal); C1q immune complexes were not detected in the serum, complement was normal, renal function was normal. Ultrasound showed an obstruction above the bifurcation of the aorta. Aortography was characteristic of Takayasu's arteritis of type II. There was narrowing of the thoracic aorta associated with a saccular aneurysm (Fig. 1) with incomplete occlusion of the abdominal aorta below the renal arteries and well formed collaterals (Fig. 2).

Management

In view of the already serious involvement of the aorta with persisting disease activity as judged by fever, ESR, and raised immunoglobulins, it was considered justifiable to give cytotoxic treatment. Chlorambucil 0·15 mg/kg was added to the regimen of prednisolone at 10 mg on alternate days. After 14 days of this regimen, the ESR had subsided to 31 mm in 1st hour and the child was apyrexial. She returned home and has continued to do well.

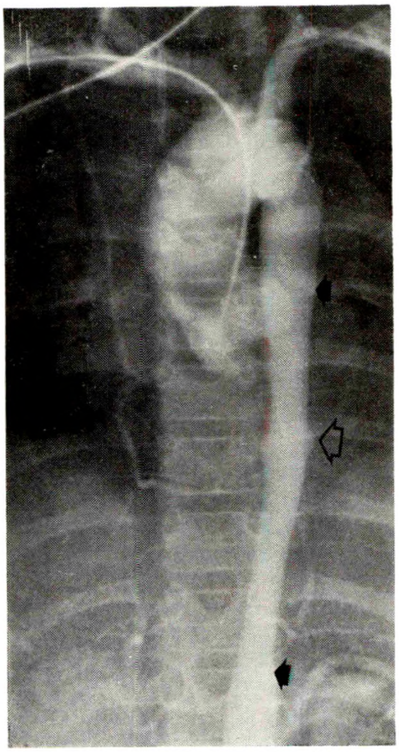

Fig. 1 *Thoracic aortogram. The descending thoracic aorta is diffusely narrowed over a long segment (closed arrows). A small saccular aneurysm is noted (open arrow). All the great vessels are present.*

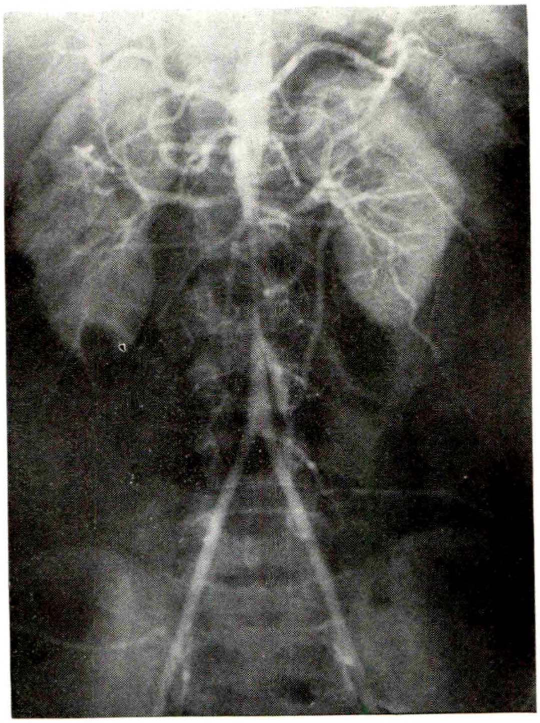

Fig. 2 *Abdominal aortogram. A long segment of the abdominal aorta is diffusely narrowed. Good flow to the iliac arteries is established through mesenteric collaterals.*

Discussion

Takayasu's arteritis is a rare inflammatory disorder affecting the aorta and large arteries in a patchy distribution. It occurs predominantly in females in the 2nd and 3rd decade, although there are several reports of cases presenting in childhood (Lupi Herrera *et al.*, 1977). The pathogenesis is uncertain but autoimmune and infectious causes have been suggested. The pathological changes consist of inflammation in all layers of the wall of the aorta with pronounced intimal thickening. Fibrosis occurs with subsequent narrowing and occlusion of the lumen, and aneurysm formation at weaker areas.

Strachan (1964) has divided the disease process into an acute systemic or prepulseless phase, and a chronic pulseless phase. The systemic phase, which may last for a period of months or years (Strachan *et al.*, 1966), is manifested by a raised ESR and a variety of symptoms suggesting connective tissue disorders. As the pathological process continues, the obstructive or pulseless phase becomes apparent with symptoms such as claudication, weakness, and parasthesiae.

Definitive diagnosis is made at either stage of the illness by arteriography which shows narrowing and/or dilatation of the aorta and its branches. Constrictions of the aorta may be short and segmental or long and diffuse, the latter being common in children in whom the abdominal aorta is often involved. Lande and Rossi (1975) suggested that in this age group the fibrosis limits the growth potential of the aorta, which can then not expand normally, leading to narrowing of the vessels with persistent and often increasing claudication.

The role of corticosteroids and immunosuppressive drugs in treatment of Takayasu's arteritis is not well defined although several reports suggest corticosteroids may prevent progression (Kawai *et al.*, 1978). Should activity not be controlled, particularly in children, in view of a possible aorta growth problem, cytotoxic drugs should be added in an attempt to reduce destruction by the inflammatory process.

This case re-emphasises the need for caution in diagnosing systemic JCA, particularly when joint involvement is inconspicuous. Better identification of the limb pain as ischaemic rather than myositic or arthralgic would have led to earlier diagnosis of the disease process in this case.

I thank Dr R. Wilkins, for performing the aortogram, and Dr B. M. Ansell for permission to describe this case.

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Archives of Disease in Childhood, 1979, **54**, 801–806

Paediatric Research Society

Aberdeen, 23 and 24 March 1979

How accurate is test-weighing? M. F. Whitfield (introduced by L. S. Taitz). Jessop Hospital for Women, Sheffield.

This study attempted to quantify the error in test-weighing using standard baby scales and ward personnel. Standard Salter 'Trent' baby scales were used to test-weigh 100 bottle-fed infants (mean weight 2·9 kg, range 2·2–4·9), the feeding bottles being similarly weighed, before and after feeding, on a Metzler laboratory balance. The measurements were carried out by nursing staff who normally carry out such measurements.

The systematic weighing errors (1 SD) in test-weights (TW) and feed weights (FW) were evaluated as 13·4 g (100 measurements) and 0·1 g (125 measurements) respectively. Four results were discarded because the TW exceeded the FW by more than 2-fold. In the remaining 96 measurements FW (± 1 SD) was 62·1 ± 16·4 g (range 25–100) and TW 57·24 ± 22·86 g (range 10–130). 32% of the TW was within 10% of the FW; 44% of the TW underestimated FW by more than 10%, one by as much as 87%, and 24% of TW overestimated FW by more than 10%. 73% of the TW was within ± 30% of FW. The regression line TW = 0·77655 FW + 9·02965 calculated for 96 points was not significantly different from TW = FW. At test weights of at least 60 g no significant differences between TW and FW were found, although there was considerable scatter of results (1 SD of FW = 10 g). At TW below 60 g TW underestimated FW significantly (TW = 40 g, n = 26, P<0·001, TW = 20 g, n = 5, P<0·01). The magnitude of the mean TW error was independent of body weight but the error as a percentage of feed weight was greatest in the 2–2·5 kg infants (30%).

It is concluded that test-weighing with standard baby scales at one feed is an inaccurate guide to feed intake, the error increasing in those taking least milk.

Steady-state phenytoin kinetics in children determined from saliva. G. W. Rylance, T. A. Moreland, and R. G. Fowles. Department of Child Health, Ninewells Hospitals, Dundee.

Phenytoin has been widely used in children for many years, but there is little information about its pharmacokinetics in a steady-state. The results of one study suggest that fluctuation in plasma concentration is clinically acceptable if the drug is given once daily (Buchanan *et al.*, 1973). We used saliva phenytoin levels, which show a good correlation with plasma levels in adults (Cook *et al.*, 1975), to determine kinetic data and to assess a once-daily dose regimen. Mixed saliva was collected from 6 children (aged 6–13 years) in a steady-state on a once-daily (0800 h) dose-frequency regimen. Samples were collected at hourly intervals from 0800–2000 h on day 1 and at 0800 on day 2 and assayed by RIA.

The mean half-life was 12·3 h (range 5·0–20·2), the mean clearance was 0·067 l/kg per hour (0·028–0·130), and the mean apparent volume of distribution was 1·15 l/kg (0·29–2·56). The mean steady-state saliva concentration was relatively low, being 2·07 μmol/l (0·77–4·78) on a mean dose of 6·42 mg/kg (4·2–9·7), and the fluctuation in concentration ranged from 152·2 to 363·2%.

The wide interindividual variation in drug elimination rate and the large fluctuation in concentration suggests that dose regimens should be individualised and that once-daily administration is unlikely to be acceptable. Saliva concentration profiles are a convenient and effective means of assessing dose-frequency regimens and investigating drug pharmacokinetics in children.

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Hydroxykynurenine hydroxyanthranilic acid ratios in children with febrile convulsions. J. McKiernan, D. Mellor, S. Court, and J. Edson, Department of Child Health, University of Nottingham.

Detection of evidence for demyelination in childhood leukaemia. T. Eden, J. B. Millar, M. Giles, N. Belton, and W. S. Uttley. Royal Hospital for Sick Children, Edinburgh.

Increasing awareness of the potential toxicity of

CNS irradiation and intrathecal medication has led to studies on psychometry and CAT scanning after such treatment. Less interest has been focused on the biochemical changes within the brain and CSF. There have been studies showing disturbance of protein, glucose, and various enzymes during and after treatment. Raised CSF levels of creatine phosphokinase (CPK) have been reported as in neurodegenerative disorders. In one study procoagulant activity in CSF was shown to be increased during CNS prophylactic treatment, and in some patients this remains permanently raised. This activity is probably due to the presence of a lipoprotein factor, derived from myelin breakdown. Combining cytology of CSF with estimation of protein, glucose, CPK, and procoagulant activity on patients receiving CNS prophylaxis, patients with meningeal relapse, and those off therapy, we have confirmed disturbances most notably of procoagulant activity suggesting demyelination. Persistence of the process once all treatment has stopped does appear likely in some cases. We discuss the potential use of measurement of myelin basic protein and 2′, 3′-cyclic nucleoside monophosphate phosphodiesterase (CNP) as more accurate methods of determining disturbances of myelination. All these estimations have practical applications in assessment of the degenerative disorders as well as in leukaemia.

Concept of nonepileptic 'anoxic' seizure threshold and its relation to age. J. B. P. Stephenson. Royal Hospital for Sick Children, Glasgow.

Approximately 130 children had seizures induced by ocular compression in the supine position, as a diagnostic and therapeutic measure in provoked convulsions. The relation of the duration of asystole to the duration of EEG flattening, if present, allows mathematical derivation of 'anoxic' seizure threshold. This threshold is low in early childhood and increases with age.

Assessment of oral therapy in vitamin B12-responsive methylmalonic acidaemia. I. Auchterlonie, G. Russell, Hazel Thom, and D. J. Lloyd. Department of Child Health, University of Aberdeen.

Methylmalonic acidaemia may occur secondary to the impaired synthesis of 5′-deoxyadenosylcobalamin, a cobamid which acts as the coenzyme of methylmalonyl CoA mutase in the conversion of L-methylmalonyl CoA to succinyl CoA. Supplementation of these patients with vitamin B12 leads to an increase in holoenzyme activity and consequent fall in the levels of methylmalonic acid and improvement in the clinical condition. Due to the high doses of B12 required, parenteral administration has been used as first choice, and the oral route is regarded as unsatisfactory. Two recent reports suggest that this latter opinion may no longer be valid, but successful experience with oral treatment remains very limited.

The case is reported of a boy now aged 2½, diagnosed as having methylmalonic acidaemia at age 7 months after admission with severe dehydration and acidosis precipitated by infection. There was a 6-month history of vomiting and failure to thrive. Diagnosis of methylmalonic acidaemia was based on both increased urinary output of methylmalonic acid (21 mmol/l) and impaired propionate/methylmalonate metabolism in skin fibroblasts. Treatment with parenteral B12 produced a rapid and complete clinical recovery and he was maintained on intramuscular B12 1 mg weekly. At age 2 he was gradually changed on to increasing doses of oral B12 and is at present receiving 4 mg daily with a g/g creatinine ratio of 3 on a 2 g/kg protein intake.

Serial measurements of lung mechanics and thoracic gas volume for babies born vaginally and by caesarean section. A. W. Boon. A. D. Milner, and I. E. Hopkin. Department of Child Health, Nottingham University.

Previous studies have demonstrated differences in the lung volumes of babies born by caesarean section, compared with those born vaginally, in the first 6 hours (Milner *et al.*, 1978). The study was undertaken to determine the time for the lung mechanics and thoracic gas volume (TGV) of babies born by section to reach the values of vaginally-born babies.

Serial measurements of lung mechanics and TGV were made in 15 babies born by elective section, and results compared with those of 31 babies born vaginally. The most striking difference was in TGV in the two groups. During the first 48 hours after delivery TGV in the babies born by section approached that of the vaginally-born babies. There was also a tendency for the section babies to have higher resistances and lower compliances than the vaginally-born babies, these differences disappearing after 48 hours.

The differences in the section babies are attributed to an increased volume of lung fluid which is gradually absorbed by pulmonary lymphatics.

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Posture and ventilation in low birthweight infants. A. A. Hutchison, K. R. Ross, and G. Russell. Department of Child Health, University of Aberdeen.

In two groups of healthy low birthweight infants, one preterm and one light-for-dates, respiratory mechanics was measured in the prone, supine, and right lateral postures. No difference due to posture were noted in the light-for-dates group.

In the preterm infants the values for elastic work, inspiratory viscous work, total viscous work, total work of breathing, tidal volume, and minute volume were greater in the prone position than in the supine. There was no difference between those results obtained in the lateral position and those in the prone and supine. Thus, in comparison with the supine position, the prone but not the lateral position resulted in an improvement in ventilation. The prone position is recommended for healthy preterm infants.

Small bowel mucosal changes in asymptomatic children with coeliac disease on gluten-free diets. P. J. Congdon, J. M. Littlewood, A. Crollick, and M. K. Mason. Department of Child Health, St James's University Hospital, Leeds.

33 asymptomatic children with biopsy-proved coeliac disease were re-evaluated while on a gluten-free diet. They had been referred from paediatricians for repeat jejunal biopsy and at this time their degree of gluten withdrawal was assessed by a dietitian. Certain laboratory investigations were also made to see if mucosal relapse could be predicted.

Of 33 intestinal biopsies only 15 were normal and 8 showed evidence of severe partial villous atrophy or subtotal villous atrophy. 10 kept to a strict gluten-free diet (GFD), but 12 admitted to frequent dietary lapses. Those on a strict GFD generally had normal biopsies (8/10) while 9 of 12 with regular dietary lapses had abnormal jejunal biopsies. Blood folate and 1-hour xylose levels failed to detect those with persisting mucosal abnormalities. It is advised that close liaison be maintained with a dietitian, and as continued gluten ingestion may be harmful, that repeated intestinal biopsies should be obtained to identify those with confirmed histological abnormalities.

Lactose malabsorption assessed by hydrogen breath testing in acute gastroenteritis. A. J. Gardiner, M. J. Tarlow, I. Sutherland, and H. G. Sammons. Department of Paediatrics and Child Health, University of Birmingham, and Department of Clinical Chemistry, East Birmingham Hospital.

Lactose intolerance is described as an important feature of acute gastroenteritis. Its frequency in infant gastroenteritis in Western society is unclear, although it appears to be of major significance in developing countries (Lifshitz *et al.*, 1971).

Hydrogen breath testing has been validated in adults as a technique for diagnosing sugar malabsorption (Newcomer *et al.*, 1975). After a sugar load, bacteria in the terminal ileum and colon metabolise unabsorbed sugar, releasing hydrogen which diffuses through the gut wall and is transported to the lungs, from where it is excreted in the breath. 43 breath tests were performed on 38 infants with clinically diagnosed acute gastroenteritis. The infants were studied at 0–32 days after the onset of the illness, at a time when they were still thought to need hospital treatment. In 9 cases a bacterial or viral pathogen was isolated from the stools.

An initial group of 20 children was given a lactose load of 0·5 g/kg. None of the children had symptoms of lactose intolerance, but 3 showed a rise in breath hydrogen. After this, 18 children were tested with a conventional lactose load of 2 g/kg. One demonstrated an increase in stool frequency, and the stools contained 0·5% reducing substances on Clinitest. Eight of the 16 children showed a rise in breath hydrogen. In none of these was any clinical symptom detected.

We conclude that clinical lactose intolerance is appreciably less common than biochemical evidence of lactose malabsorption in infant gastroenteritis as found on hydrogen breath testing. Our experience suggests that it is of less significance in Birmingham than reports of tropical infant gastroenteritis would suggest. Management regimens in temperate, developed countries should therefore be modified from those used in the tropics.

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Raised hepatic copper concentration in Indian childhood cirrhosis. M. S. Tanner, B. Portmann, C. F. Mills, and A. P. Mowat. St George's Hospital and King's College Hospital, London, and the Rowett Research Institute, Aberdeen.

Indian childhood cirrhosis (ICC) is a disease of unknown aetiology, usually presenting with abdominal distension in infancy, and rapidly progressing to jaundice, ascites, hepatocellular failure, and death. We recently described a new histological feature of the disease, namely prolific coarse orcein-staining granules in both hepatocytes and proximal renal tubular cells, and suggest that these may represent copper-binding protein (Portmann *et al.*, 1978; Tanner *et al.*, 1978).

In a further series of Indian children with liver disease, in whom a clinical and histological diagnosis of ICC was made, 5 had extremely high hepatic copper content (mean 1389 μg/g dry weight; normal <55). 14 children with other hepatic diseases had normal or only slightly raised values, with the exception of one child with cholestasis in whom a value of 292 μg/g was found. We therefore suggest that ICC is caused by a grossly raised hepatic copper concentration, the origin of which may be either an abnormally high copper intake, or an inherited abnormality of copper metabolism similar to Wilson's disease. The fact that ICC is limited in its distribution to the Asian subcontinent suggests the former, an environmental aetiology. In 4 of the 5 cases, the family cooked or stored water in vessels made of brass or bittall (an alloy containing copper).

These results raise the exciting possibility that this almost universally fatal disease may be entirely preventable.

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Transpyloric feeding in 32 babies undergoing intensive care. Elizabeth Dryburgh. General Infirmary, Leeds.

Transpyloric feeding, using commercially available silicone tubes (Vygon Ltd), is described in 32 newborn infants undergoing intensive care. 30 babies required assisted ventilation; 2 had undergone surgery for upper small bowel atresia. Gestational age ranged from 26–42 weeks (mean 32). The technique of passage of the tube, and the difficulties encountered are described. Transpyloric tubes were passed on 49 occasions in 28 (94%) babies. 80 *x*-rays to confirm the tube position were required (1·7/passage, 2·3/infant). Placement of the tube at operation was carried out in 2 babies with small bowel atresia. Attempts to pass the tube were abandoned in 2 infants. The feeding tubes remained *in situ* for 1–43 days (mean 10).

During the first 7 days of life 20 infants transpylorically fed lost weight (mean 18 g/day). In the others the weight remained static. After 7 days all babies fed by this route gained weight (mean 35 g/day).

The most common complication (39%) was accidental displacement of the tube. Transient diarrhoea (23%) and vomiting (6%) also occurred. Necrotising enterocolitis was suspected clinically in 2 (6%) infants but was not confirmed by *x*-ray.

How clean does breast milk have to be for feeding raw to babies on SCBU? L. Carroll, M. Osman, and D. P. Davies. Departments of Child Health and Microbiology, Leicester Royal Infirmary.

At present there is considerable debate over the practicalities and safety of feeding pooled raw (unheated) breast milk to babies on special care baby units (SCBU) (*British Medical Journal*, 1978). Of particular concern is the bacterial contamination which might be allowed. Recently proposed bacterial criteria for feeding raw breast milk were largely empirical (Williamson *et al.*, 1978) and did not take into account the bacterial flora of breast milk which is taken by the normal breast-fed baby. 207 samples of breast milk from 70 mothers were collected in sterile universal containers by a clean-catch method. Each sample was collected between the 4th and 7th days. The mothers were not taking antibiotics nor were they applying antiseptic cream to the breasts. The milk samples were delivered to the laboratory within one hour of collection. Serial dilutions of milk between 10^{-1} to 10^{-4} were made in nutrient agar (Oxoid) using a semiautomated analyser, and after overnight incubation at 37°C the numbers of colony-form units per litre (CFU/l) were determined. 170 (82%) samples grew only skin-commensal organisms (coagulase-negative staphylococcus and *Streptococcus viridans*) in numbers ranging from 10^5–10^{10} CFU/l. 13 (6%) grew *Staphylococcus aureus*, 15 (7%) enterobacteriaceae, 3 (2%) group B streptococcus, and 6 (3%) produced no growth.

A feature of this study is the heavy bacterial contamination of breast milk taken by the normal suckling infant. We propose that milk contaminated by *S. aureus*, enterobacteriaceae, and group B streptococcus needs to be pasteurised before use, but breast milk containing only skin-commensal organisms in numbers up to 10^{10} CFU/l may be given raw.

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Prophylaxis against early onset group B streptococcal septicaemia. D. J. Lloyd, T. K. Belgaumkar, K. E. Scott, A. J. Wort, K. Aterman, and V. W. Krause. Departments of Pediatrics, Obstetrics, Microbiology, and Pathology, Grace Maternity Hospital and Dalhousie University, Halifax, Nova Scotia.

Between January 1969 and May 1974, 11 of 1208 low birthweight infants developed early onset group B streptococcal (GBS) septicaemia. All 11 infants were <35 weeks' gestational age and 9 presented with the clinical and *x*-ray signs of RDS. 10 of the 11 infants died. Antibiotics were given to 3 infants only, but not before age 12 hours. From June 1974 infants <35 weeks gestational age and from January 1977 all infants <2500 g, received systemic penicillin by 2 hours of age after throat, ear, umbilical, rectal, and blood cultures. Penicillin was continued for 10 days if GBS was isolated but was stopped at 48 hours if cultures were negative. Between June 1974 and May 1978, there was one case of septicaemia in the 1143 low birthweight infants born during this period but none has died from GBS. These data suggest that systemic penicillin from birth will prevent the mortality from GBS in low birthweight infants ($\chi^2_1 = 7{\cdot}65; 0{\cdot}01 > P > 0{\cdot}001$).

Follow-up of children of diabetic mothers. Mary Cummins and Mary Norrish. Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London.

To be published in full in the *Archives*, 1980, **55.**

Follow-up of children of mothers with chemical gestational diabetes. Anne Reid, G. Russell, H. W. Sutherland, P. D. Bewsher, and J. M. Stowers. Departments of Child Health, Obstetrics and Gynaecology, Therapeutics and Clinical Pharmacology, and Medicine, University of Aberdeen.

Three groups of children whose mothers were diagnosed as having chemical diabetes during pregnancy and who were treated at that time with chlorpropamide 100 mg daily, with insulin, or without the use of drugs, were reviewed to determine if there was any difference between these groups of children recognisable on follow-up, and attributable to the effect of maternal treatment on the fetal islets in terms of physical growth, neurological and intellectual development, and β-cell function. A control group of 43 healthy children was established for the interpretation of the oral glucose tolerance test used to assess β-cell function. The growth of these children was normal except for a slight tendency to underweight-for-height in the girls of mothers who received no treatment. No child was seriously handicapped neurologically, although 2 children were mentally retarded and required special schooling, one in the insulin group and one in the no drug group; one child in the chlorpropamide group has bilateral neurosensory deafness. There was no difference found in the intellectual ability of the three groups of children.

There appeared to be a significant impairment in glucose tolerance of children of mothers treated with insulin compared with a control group. This was not explained completely by either the age difference of the children at follow-up or the degree of maternal glucose intolerance in pregnancy. Three of the chlorpropamide group have required treatment for their diabetes.

Hormonal and auxologic patterns in boys with constitutional growth delay. M. O. Savage, J. L. Penfold, M. A. Preece, Y. Cyranka, J. Jones, and M. D. Mansfield. Department of Growth and Development, Institute of Child Health, London.

Serum LH and FSH responses to LHRH (100 μg IV) were measured in 24 boys with constitutional growth delay. Basal plasma testosterone (T), androstenedione (A), and dehydroepiandrosterone (DHA) were also measured in 16 of these children. Two groups of boys were defined: (1) prepubertal (mean chronological age (CA) 11·8 years, bone age (BA) 9·5 years, height SD score −3·2, and mean testicular volume (MTV) 2ml), and (2) early pubertal (mean CA 14·7 years, BA 12·3 years, height SD score −3·7, and MTV 3–8 ml).

Peak LH response to LHRH was greater in group 2 (mean 8·7 IU/l) than in group 1 (mean 2·9 IU/l). In 8 out of 9 prepubertal subjects with a bone age of <10 years peak LH response was <2 IU/l. There was no difference between FSH responses (4·8 and 3·8 IU/l respectively). Basal T levels were low in prepubertal subjects whereas A and DHA increased from a BA of 8 years. These findings suggest firstly, that the LHRH test is of limited value in the diagnosis of gonadotrophin deficiency in the early prepubertal period and, secondly, that a normal temporal relationship of gonadotrophin and adrenal androgen secretion with bone age is present in boys with constitutional growth delay.

Parental and medical assessment of symptoms during infancy. A comparative study of hospital admissions and unexpected home deaths. A. N. Stanton, P. M. McWeeny, A. Jay, E. Irwin, and J. R. Oakley. Princess Mary Maternity Hospital, Newcastle upon Tyne.

The symptoms and medical contacts of 150 infants surviving acute hospital admission were compared with those of 100 infants dying unexpectedly at home, with histories of major terminal symptoms. Half of each group had been ill for more than 3 days. Specific symptoms (apart from coughing) were relatively rare among home deaths, but both groups generally had nonspecific behavioural changes. The severity of the illness, with physical signs stressed more often than symptoms, determined referral in half the cases admitted after primary care assessment. 31% of these families were considered by the GP to have delayed their consultation. The remaining referrals were partially related to families' inability to cope adequately with their children's illness. Initiative for follow-up had been left to the parents in 94 (87%) of the 108 cases not admitted at first consultation, although 44% of these families already wanted their children admitted. Only 39 of the home deaths had been medically assessed, 17 within 24 hours of death, including two prearranged follow-ups. As parents often sought medical help inappropriately, and 23% of all families expressed hesitation about contacting their doctor, it is suggested that daily professional reassessment should be considered normal practice when infants have major symptoms.

Use of an objective clinical examination in assessing medical students' practical skills in paediatrics.

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The assessment of students' skill at performing certain clinical techniques has always been difficult, as examiners tend to confine themselves to standard areas—such as the detection of signs and the interpretation of data. Despite the widely held view that the ability of junior doctors in such procedures as urine testing and history taking is inadequate, these areas are seldom covered in clinical examinations which are overwhelmingly subjective in their method of appraisal.

This paper describes the results from a type of assessment not previously used in paediatrics, the Objective Structured Clinical Examination (Harden *et al.*, 1975). In this examination students rotate round a number of different stations at each of which they spend 4 minutes and perform a standard procedure—such as taking a limited history, examining one particular area, interpreting *x*-rays, or testing urine. Alternating stations assess the student's analysis of his findings by multiple-choice questionnaire; examiners also observe the student and mark his performance from a check list at some of the stations. 18 final-year students were assessed in this way and figures are shown from some questions in the examination, of which examples are given. Table 1 shows the results in 4 individual questions and Table 2 correlates these results with those in the examination as a whole. Students' performance in urine examination was particularly poor and the implications for this in improved teaching are discussed.

Table 1 *Results (abbreviated) in four questions*

Question	*Mark % (mean ± 1 SD)*
A	74 ± 11·7
B	72 ± 20·1
C	41 ± 14·5
D	74 ± 15

Table 2 *Correlation of results*

Question	*Mark %*	*r*
Total (whole paper)	75 ± 5·9	X_2
A	74 ± 11·7	0·66
B	72	0·47
C	41	0·005*
D	74	0·24

A = Examiner's check list on history of vomiting, B = MCQ on history of vomiting, C = MCQ on urine testing, D = MCQ on *x*-ray interpretation. * Significant at 0·001 level

Students learn best those subjects they know they will be examined on; this technique allows a particular area of clinical performance to be assessed objectively and it is therefore a valuable teaching aid.

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Archives of Disease in Childhood, 1979, **54**, 807–810

Correspondence

Congenital nephrogenic diabetes insipidus

Sir,

Schreiner and co-workers reported a baby girl with congenital nephrogenic diabetes insipidus (NDI) (*Archives*, 1978, **53**, 906). I should like to contribute a case diagnosed as having partial NDI.

This boy had been transferred from a local hospital at age 9 months because of high fever with high serum Na and Cl concentrations, initially noticed in the first week of life. His mother showed polydipsia and polyuria: her urine osmolality after water deprivation for 12 hours was 270 mmol/kg. Investigation of the patient showed high serum osmolality (315 mmol/kg), low urine osmolality (100 mmol/kg), serum Na 172 mmol/l, and serum Cl 126 mmol/l.

Subsequently clearance studies were performed while the boy was receiving both a normal and a salt-restricted diet, after water deprivation, and after intravenous DDAVP (Aronson and Svenningsen, 1974). The main results were: (1) On water deprivation the patient was able to concentrate urine up to 600 mmol/kg simultaneously with reduction of urine volume; after DDAVP (0·4 ml IV) urine volume decreased further; osmolar clearance, which had increased during water deprivation, decreased after DDAVP. (2) On normal diet and on salt-restricted diet DDAVP resulted in increasing osmolar and free water clearance (and urine volume).

We made the following interpretations on the effect of DDAVP (a synthetic vasopressin analogue) on our patient's kidneys: renal resistance to DDAVP was incomplete; there was an adequate response after giving DDAVP during water deprivation, whereas a paradoxical effect on osmolar and free water clearance (Brodehl *et al.*, 1965) was apparent during the control periods.

Partial NDI (McConnell *et al.*, 1977) was diagnosed and treated by salt restriction and frusemide (15 mg/day). Follow-up 3 years later shows uncomplicated physical and psychological development of the patient with normal or almost normal values for serum Na, Cl, urea nitrogen, osmolality, and bicarbonate. Urine osmolality ranged from 200 to 265 mmol/kg.

I wonder if Schreiner and co-workers would like to comment on our patient, particularly with regard to their own therapeutic experience.

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Myotonic dystrophy and bonding failure

Sir,

In their report of 5 cases of the neonatal form of dystrophia myotonica (*Archives*, 1979, **54**, 331), Pearse and Höweler emphasise the ethical problems facing the clinician once the diagnosis has been made, and they discuss the need for genetic counselling. We should like to add support to their concern for earlier diagnosis by drawing attention to another important and potentially lethal hazard run by babies with this condition—that is bonding failure. If they survive the neonatal period, these babies must always be considered to be at increased risk of rejection and neglect. Not only are they likely to have accumulated a number of the features commonly associated with child abuse—for example, neonatal separation, early ill health, maternal physical and emotional illness (Lynch, 1975; Lynch and Roberts, 1977)—but both mother and child are further handicapped by the inability to use facial expression effectively as a means of communication.

This was well illustrated by a family referred to the Park Hospital in Oxford. The parents were both very young and came from unhappy and divided homes, thus the potential for abuse was high. The mother's relationship with her own mother was hostile yet dependent, and the father had experienced a rigid authoritarian upbringing. When we met the mother she was just 20 and had had two caesarean sections within 13 months. Her second son had been very ill in the neonatal period, spending the first 7 weeks of his life in the special care baby unit. He had required assisted ventilation for some days. During his stay in the unit the diagnosis of myotonic dystrophy was made both in himself and his mother. A distaff family history of dystrophia myotonica was discovered, with the mother's own mother, the grandmother, and a great aunt suffering from cataracts and facial diplegia. It was also found that the elder brother had a milder form of the disease.

When finally discharged home, the baby had a floppy, expressionless face; he made none of the grimaces and little noises a normal baby makes. His abnormal cry was quiet and ineffective; his smile did not appear. Feeding was a nightmare. Much of his time he slept 'like a dead baby', making him easy to 'forget' and his mother was terrified that he would die silently without her noticing. She was at a further disadvantage by her own inability to use facial expression as a means of communication with her baby. Soon all those concerned in the baby's care, including the mother herself, were fearful for the baby's safety and help was sought before there was serious neglect or abuse.

The family were then admitted to the Park Hospital for an intensive period of treatment where the mother learned to make appropriate signals and respond to her baby. Both mother and child could gaze fixate, even though it could not be coupled with smiling. Starting from this, the mother was helped to recognise the more subtle signs from the baby, such as tiny mouth movements and slight panting sounds in her presence. The baby, too, was encouraged in making chuckling noises in response to his mother's gaze. Marital therapy was also required and it was interesting to note that in the mother's family all the sufferers of myotonic dystrophy had had broken marriages. Several years later, this family remains united but the parents still require help from both health and social services in bringing up their 2 young handicapped children.

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Early use of sodium nitroprusside in respiratory distress syndrome

Sir,

Beverley *et al.* (*Archives*, 1979, **54**, 403) reported the response to sodium nitroprusside in an infant with hyaline membrane disease, and I should like to make some comments on their patient.

The course of the illness, with the infant not requiring added oxygen and only very low ventilator pressure by 24 hours of age, must cast doubt on the diagnosis of surfacant-deficiant hyaline membrane disease, and suggests that the baby was suffering from the after effects of severe birth asphyxia, the early problems of intrapartum pneumonia, or perhaps from some iatrogenic disease.

During the time sodium nitroprusside was being infused, 3 other major changes in treatment took place which may have been responsible for improving the baby's condition. Firstly, his pH was corrected. The effect of this on pulmonary perfusion and pulmonary vascular tone is well known, and could itself be responsible for the improved oxygenation in the infant. Secondly, the inspiratory to expiratory ratio was reduced from 4:1 to 1·5:1 and while we do not know the ventilator pressures that were sustained during this period, it seems likely that this would be associated with a considerable fall in the mean airways pressure. Particularly in infants without hyaline membrane disease, a high mean airways pressure can be responsible for serious pulmonary underperfusion, and lowering the airways pressure as was done in this patient, can be associated with a large increase in arterial Po_2. Thirdly, they transfused their patient, and while we are given no blood pressure data before this was started, the fact that they were able to increase the baby's blood volume by more than double suggests that, irrespective of the hypotension-producing effect of the nitroprusside, the infant was previously hypovolaemic or hypotensive, or both. Correction of that could also be responsible for an improvement in the infant's condition and oxygenation.

I would submit therefore that Beverley *et al.* have provided absolutely no evidence for a beneficial effect from sodium nitroprusside in their patient, and that before this comparatively dangerous drug is used, evidence that it improves oxygenation while other factors in the treatment are held constant is required. This, for example, has been provided for tolazoline (McIntosh and Walters, 1979).

Reference

McIntosh, N., and Walters, R. O. (1979). Effect of tolazoline in severe hyaline membrane disease. *Archives of Disease in Childhood*, **54**, 105–110.

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Sir,

The letter from Beverley *et al.* (*Archives*, 1979, **54**, 403), and the report by Abbott *et al.* (1978) to which they refer, should both be treated with extreme caution. In neither is a good case made for the use of sodium nitroprusside to reduce pulmonary vascular resistance (PVR) in severely hypoxic newborn babies. While Beverley and colleagues refer to the known hazards of this hitherto untried drug, they give no details of the state of the circulation or of the $Paco_2$ during their infant's first few hours. These are important since poor tissue oxygenation and hypercapnia may both contribute to acidosis, and PVR in the newborn may be expected to increase as pH falls (Rudolph, 1977). The extreme acidosis at 2–4 hours of age was presumably the legacy of severe birth asphyxia.

Nevertheless, the information provided suggests that after a blood transfusion (which should have improved tissue oxygenation) and during the slow correction of the severe acidosis, there was initially a steady fall in right-to-left shunt, followed at the age of 11 hours by a more rapid improvement in both the arterial pH and $Paco_2$.

There is no evidence that sodium nitroprusside had any effect other than, possibly, to cause systemic hypotension. Similarly, the paper by Abbott *et al.* (1978) merely serves to illustrate the importance of correcting acidosis and hypercapnia early in the course of neonatal respiratory distress. Moreover, their case illustrates the ill-advised use of sodium bicarbonate as a buffer in a hypercapnic neonate whose minute ventilation is fixed by mechanical ventilation. Their figure clearly shows a *worsening* of hypercapnia and a *fall* in pH after bicarbonate infusion.

It is clear that the primary aim of therapy in severely hypoxic neonates suffering from RDS should be to attempt to correct those metabolic derangements which promote pulmonary vasoconstriction. It would be dangerous to conclude from the currently available literature that sodium nitroprusside has any value in such patients.

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Dr Beverley and co-workers comment:

The clinical and radiological appearances in the small preterm baby we described gave us a working diagnosis of RDS, and contrary to Dr Roberton's impression we stated that at 24 hours old the baby still required added oxygen as well as intermittent positive pressure ventilation (IPPV). We accept that birth asphyxia may have contributed to the severity of his illness.

We agree that correction of metabolic derangements which may provoke a rise in pulmonary vascular resistance (PVR) is important in the management of RDS and are sure that increasing Pa_{O_2} and tissue oxygenation is of paramount importance in making this correction. In our case correction of arterial pH was unlikely to have been due to bicarbonate infusion, as <1 mmol bicarbonate had been infused by 12 hours of age when the baby's arterial pH was 7·4. We agree that injudicious use of bicarbonate may be detrimental. Hypercapnia was not a significant contributory factor to the acidosis nor was the high PVR. Pa_{CO_2} in our baby ranged from 3·5 to 6·4 kPa (26·3 to 48 mmHg) during the period of IPPV. Neither was hypovolaemia or hypotension before the use of nitroprusside suggested by continuous measurement (via the umbilical artery catheter) of arterial blood pressure, by the small core-peripheral temperature gradient, or by the failure to improve after the initial 20 ml transfusion at 4 to 5 hours old. The subsequent transfusions were given over a 5-hour period in response to downward trends in arterial blood pressure and widening core-peripheral temperature gradients after starting nitroprusside.

We wish to emphasise that the ventilator settings at the start of the nitroprusside infusion were those which produced the maximum Pa_{O_2} and that subsequent changes were made in response to improvements in the infant's condition and were not the cause of them.

We accept that it is advantageous when studying the effects of a drug to keep other factors in the treatment constant, but this may not be possible when the drug is being infused over a period of time and may indeed be contraindicated.

Our original letter drew attention to the possible toxic effects of nitroprusside and stressed the need for careful biochemical and blood pressure monitoring during its use. Since then we have used nitroprusside in 5 other infants with severe RDS with beneficial effects in all cases and feel that further study of its use in this condition is warranted.

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Role of gastrin in pyloric stenosis in infants

Sir,

The careful clinical study by Hambourg *et al.* (*Archives*, 1979, **54**, 208) evaluating serum gastrin levels in infants with hypertrophic pyloric stenosis adds further evidence minimising the role of gastrin in the production of this disorder. Although Hambourg *et al.* quite properly indicate that there is controversy about preoperative fasting gastrin levels in infants with hypertrophic pyloric stenosis when compared with controls, most authors have agreed that there is no significant increase of this hormone. Two major questions remain unanswered: (1) Is there excessive *in utero* exposure to gastrin in these infants? (2) Is there a possibility of excessive postprandial hypergastrinaemia in these infants? The first question has been addressed by a study (Werlin *et al.*, 1978) in which levels of circulating gastrin were measured in umbilical venous blood and maternal venous blood obtained at delivery in 40 infants who subsequently developed hypertrophic pyloric stenosis. In this comparison, there was no significant difference between the mean cord and maternal gastrin concentrations of infants subsequently developing pyloric stenosis, and normal infants. The possibility of excessive postprandial hypergastrinaemia in these infants was addressed in a recent clinical study from our institution (Moazam *et al.*, 1978), and has been confirmed by Hambourg's work. In our study, 11 patients with congenital hypertrophic pyloric stenosis were evaluated with sequential pre- and postprandial serum gastrin levels immediately before pyloromyotomy and 2 to 10 weeks later. When compared with an age-matched control, the fasting gastrin levels in our patients (125 ng/l) were identical with the control (128 ng/l). The gastrin responses to a Sustagen meal (providing 1·7 g/kg protein) were likewise similar. The finding of a somewhat flattened postprandial gastrin curve in Hambourg's infants after pyloromyotomy is most likely explained by residual antral stasis. As these authors properly point out, radiological evidence of impaired gastric emptying frequently persists in the immediate postoperative period in these patients. We would agree with the conclusions of these authors that there is no evidence to support the hypothesis that patients with pyloric stenosis have an abnormal gastrin mechanism.

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Dr Hambourg and co-workers comment:

We agree with the conclusions of Dr Rodgers and Dr Moazam although the results of their recent study are not comparable with ours (Moazam *et al.*, 1978). Regarding the curve showing changes in serum gastrin levels after ingestion of a high protein meal (Sustagen, providing 1·7 g/kg protein) these authors obtained a slope that increased more slowly from baseline values. Moreover the peak gastrin values were noted in control infants at 45 min, and in patients with hypertrophic pyloric stenosis at 30 min preoperatively and 45 min postoperatively. Analysis of the decreasing slope was not described. Our study was performed by administering a casein hydrolysate (Amirige, providing 0·7 g/kg protein) containing free amino-acids. In 11 control infants and 10 patients with pyloric stenosis the mean peak gastrin level was noted within the first 10 minutes after the feeding, showing a maximum value at 10 min and a return to basal gastrin levels after 60 and 90 min. The differences may be explained by differences in the two methods. Certainly high protein preparations are capable of producing a gastrin release. However hydrolysed proteins, especially free amino-acids, were found to be more potent gastrin stimulants (Elwin, 1974), thus increasing the accuracy of the test. Our results with the gastrin secretion test show the importance of recording the serum gastrin levels within the first 10 min after feeding and continuing to record it for at least 60 min. In the study by Moazam *et al.* (1978), 11 infants with pyloric stenosis were evaluated with postprandial serum gastrin levels before pyloromyotomy and 2 to 10 weeks after surgery. Interestingly, a gastrin secretion test was performed on patients with untreated hypertrophy of the pylorus. In the postoperative studies a similar rise in serum gastrin concentration was noted in response to protein ingestion, however no significant differences were observed from preoperative studies.

In our patients, increased fasting gastrin levels were noted after pyloromyotomy and were still present 2 weeks after the operation. The postoperative hypergastrinaemia may be explained by a residual antral stasis on the 7th and 15th days after surgical pyloromyotomy, represented by a postprandial gastrin curve with a 'levelling-off' effect between 30 and 60 min, as Dr Rodgers and Dr Moazam clearly point out. Nevertheless, in these two studies test meals did not produce an exaggerated gastrin response, and the results were of the same order as those obtained by the same trial control stimulation. Therefore we agree that there is no evidence that patients with pyloric stenosis have an abnormal gastrin mechanism.

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rchives of Disease in Childhood, 1979, 54, 811–812

Book reviews

Colour Atlas of Clinical Conditions in aedodontics. By R. Rapp and G. B. inter. (Pp. 142; illustrated. £12.00 rdback.) Wolfe: London. 1979.

his is the first coloured diagnostic atlas paediatric dentistry to be published. It is ot meant to be comprehensive but a sual guide to many abnormalities and seases of the hard and soft tissues ncountered in the oral and facial uctures of children and adolescents.

The opening chapter is divided into ctions based on the anatomical features f the head and is largely concerned with evelopmental anomalies of the cranium d face. With the aid of excellent colour ictures and *x*-rays, it illustrates a series of normal conditions with their variations, ch succinctly described in brief accompanying paragraphs giving the salient atures.

The second chapter is the longest and overs abnormalities of the teeth with eference to number, size, shape, structure, d colour. Although some sections may e of greater interest to paedodontists, aediatricians will find the beautifully lustrated descriptions of anomalies of oth structure and colour especially luminating as a number of these are trogenic. The coverage of gingival and eriodontal conditions in chapter 3 is good ut may prove confusing if taken in olation. Chapter 4 deals with the lips, lveolar mucosa, cheeks, and floor of outh including congenital, infective, and aumatic conditions. Many of the lustrations amplify conditions partially escribed in earlier sections. Except for the ection on clefts, chapters 5, 6, and 7 erely add a little to the diagnostic pictures lready seen and are probably of greater nterest to dentists.

It was an inspired act to have a chapter n the limbs. The illustrations and content eally do fulfil the authors' intention hat '. . . . they either complete a clinical icture of, or are closely related to . . . .' onditions already described in the atlas.

It would be wrong to claim that this ook is above criticism, especially for the aedodontist who may feel it is incomplete nd wishes it contained some rather more haracteristic examples of certain conditions. Nevertheless, it should prove an excellent book for medical and dental students and clinicians, providing an easily usable reference book to assist in the recognition and diagnosis of oral and dental disease.

EILEEN C. JAFFE

British Paediatric Association Classification of Diseases (in two volumes). By BPA. (Vol. 1: Pp. 220. Vol. 2: Pp. 94, index. £4.00 for the two volumes, paperback.) BPA: London. 1979.

There must be people for whom the classification of disease represents the ultimate challenge of scientific medicine. As one who is happy to leave all classification to others, I approached these volumes with trepidation.

The aim of the Health Statistics subcommittee of the BPA in preparing the new classification of diseases was to design a supplement compatible with the ninth revision of the WHO *International Classification of Diseases*, but modified to be of use specifically in paediatric and neonatal departments. The 3-digit main *ICD* code is followed by a 1- or 2-digit subcode. The first 4 digits of the code in the paediatric supplement are compatible with the *ICD* and only the fifth digit is specific to the paediatric classification. It is pointed out in the introduction that the general use of such a unified coding system will greatly facilitate data retrieval for preparation of health statistics or research purposes.

The first volume shows the layout of the codes and is divided into 16 chapters according to type of condition, areas of the body affected, or stage of life at which a condition may occur. The second volume comprises an alphabetical index of diseases with the appropriate codes. For coding purposes the alphabetical index alone should be sufficient, although it is intended that it will be used in conjunction with the main *ICD*.

The new supplements are far more comprehensive than the old *Cardiff Diagnostic Classification* which they replace. However, the only test of such a classification is to determine how easily and efficiently it can be used in practice.

Unfortunately I ran into trouble on my first attempt to use it for coding disease in the newborn because there are no codes appropriate for periventricular leucomalacia. As this is one of the most common and important forms of brain damage in preterm infants and is now diagnosed in life using computerised axial tomography it seems a pity that there is no code for it. Other codes were found moderately easily as soon as the quirks of the index were recognised. The dislike of compilers for multi-indexing means that the structure of a particular index has to be understood before it can be used. In this one for instance, rhesus iso-immunisation appears under 'incompatibility—(blood)', and hyaline membrane disease under 'syndrome—respiratory distress (idiopathic)'. This is extremely irritating to the occasional user like myself who would prefer an alphabetical list three times as long that would enable him to find a condition under whichever name he cared to look, rather than having to guess where it will have been listed. The index will however prove stimulating to clerical staff who revel in the nuances of inside-out alphabetical listing and may even learn to code periventricular leucomalacia under 348·1 ('Anoxic brain damage. Excludes: when of newborn'), until the next revision is published.

Despite these criticisms the codes do represent a worth-while advance and should of course be introduced by all paediatric departments. If users keep the BPA informed of any problems they encounter there may be hope that, in the future, an optional idiot-proof version will be made available for those of us who find indices difficult to use.

J. S. WIGGLESWORTH

Liver Disorders in Childhood. Postgraduate Paediatrics Series. By A. P. Mowat. (Pp. 407; illustrated + tables. £18.50 hardback.) Butterworth: London. 1979.

I have been able to assess the usefulness of this book as a source of clinical reference in dealing with the relatively small numbers of hepatic problems coming my way. It is predictably good, both because Alex Mowat writes from a depth and breadth of experience of paediatric liver disorders unique in this country, and because he writes well.

It is a pleasantly compact volume to handle, the print and reproductions are clear, and it is well illustrated with photomicrographs, line drawings, and clinical photographs. References are generous and some as recent as 1978 are included.

Two introductory chapters discuss the anatomy and physiology of the liver and biliary tract, perhaps a little too briefly. Hyperbilirubinaemia, conjugated and unconjugated, is the subject of the next two chapters. Clinical conditions giving rise to jaundice in infancy are clearly set out, and by using the tables and checklists of possible diagnoses, the general paediatrician is unlikely to overlook treatable causes of the neonatal hepatitis syndrome. Practical advice on a suitable and humane programme of investigation is given, including a basic outline of surgical techniques for appropriate cases.

Subsequent chapters deal with infections: hepatic failure, Reye's syndrome (an excellent review and guide to management), toxic and metabolic disorders, genetic, structural, and biochemical disorders, cirrhosis, cystic fibrosis, tumours, and vascular abnormalities. The developing world is not forgotten, and specific chapters deal with sickle-cell anaemia and Indian childhood cirrhosis. I particularly appreciated the final chapters in which methods of investigating liver and biliary function are discussed.

There are an irritatingly large number of typographical errors: for example on p. 59, phenobarbitone is referred to as an enzyme 'reducer' when 'inducer' was surely intended. The index is mainly adequate, but it eschews some eponyms in common use (for example, Alagille disease, Byler disease) whose correct titles are long and difficult to remember, and therefore to find. There will surely be further editions in which these small defects can be remedied. At £18.50, reasonable in 1979, this book is an excellent investment. It has been worth waiting for.

J. A. DODGE

Pediatric Orthopedic Radiology, volume 15 in the series Saunders' Monographs in Clinical Radiology. By M. B. Ozonoff. (Pp. 516; illustrated. £22.50 hardback.) Saunders: Eastbourne. 1979.

I am sure that most radiologists' hearts sink when they are faced with an awkward problem in paediatric orthopaedic radiology, The trouble owes much to the fact that the two disciplines have so little in common that the respective specialists are not aware of the others' difficulties.

Dr Ozonoff is in a unique position to bridge the gap between the orthopaedic surgeon and the radiologist: he is Director of Radiology at Newington Children's Hospital in Connecticut and has also had experience in orthopaedic surgery.

The book catalogues the disorders of childhood which affect the skeleton, the first chapters dealing with specific parts of the skeleton and the later ones with generalised disorders. This makes for easy use of the book: none of the searching that bedevils reference to books written by committees is necessary. Most of the sections on specific disorders are masterpieces of brevity and lucidity. The current thinking is presented with relevant recent references. Indeed many sections could be read with equal reward by orthopaedic surgeons or radiologists.

The section on the normal hip is most valuable. The host of measurable variants, lines, angles, and levels are described and, what is most important, their significance is given due weight. One or two readers may baulk at the lines drawn along the femoral shafts to show the Von Rosen sign in Figs 3–8 B but this must not be allowed to detract from the overall impression of reliability; I am sure the section will be used to settle many viewing-room arguments. Hip arthrography in congenital dislocation discovered late is strongly advocated. There are few who would condemn this procedure out of hand, but many British surgeons feel that the information gained is frequently spurious and that the extra irradiation is only justified in cases of unusual difficulty.

The book is densely packed with information and cannot be read quickly. It is a work of reference of remarkable authority and depth. It will prove a most valuable book to radiologists and orthopaedic surgeons who deal with children.

MICHAEL WATSON

Toys and Playthings in Development and Remediation. By J. and E. Newson. (Pp. 279; illustrated. £1.50 paperback.) Penguin: Middlesex. 1979. A hardback edition, price £7.95, is available from All
and Unwin: London.

In their latest book John and Elizabe
Newson have taken a long and detail
look at the part played by toys in t
developmental progress of young childre
The book itself is virtually in two par
The first and longest part describes
fascinating detail for parents and pr
fessionals in child development t
importance of play, 'perhaps the mo
serious and significant of all hum
activities'. The message which comes ov
very clearly is that play for the infant a
young child is essentially social commu
cation. Toys are no more than pegs
which to hang our play and serve
structure the child's experience. Develo
ment of fine manipulative skills, spee
and language, the growth of role a
fantasy play, and of concepts and abstra
thinking need continuing social exchang
with a caring adult. It is compelli
reading, not only for parents but f
doctors, hospital nurses, nursery nurse
therapists, and others who work wi
young children.

The second part of the book on play a
playthings for the handicapped child
perhaps less successful. A chapter
using toys for assessment seems almo
irrelevant in the context of this book.
discussion on problem-orientated a
developmental approaches to the remedi
use of toys is of interest to therapists, b
for parents of a severely handicapp
child the problem often is that the chi
simply does not play. Drive and a will
achieve may often be quenched in blin
physically handicapped, or autist
children because the handicapping con
tion prevents them from reaching the
true potential. The authors describe the
problems very clearly but offer little
practical terms to parents on how to cop
A later section in which three severe
mentally handicapped children wi
obsessional traits and mannerisms a
described in anecdotal form gives usef
guidelines on management if a one-to-o
relationship with a therapist can
maintained in a selected environment ov
a period of time.

John Holder's drawings are a delightf
addition to a book which deservedly w
be widely read.

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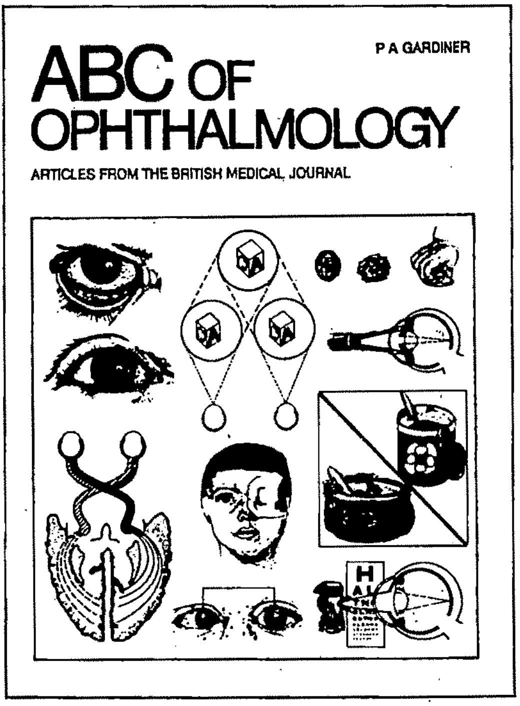

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Organ der Deutschen Gesellschaft für Kinderheilkunde

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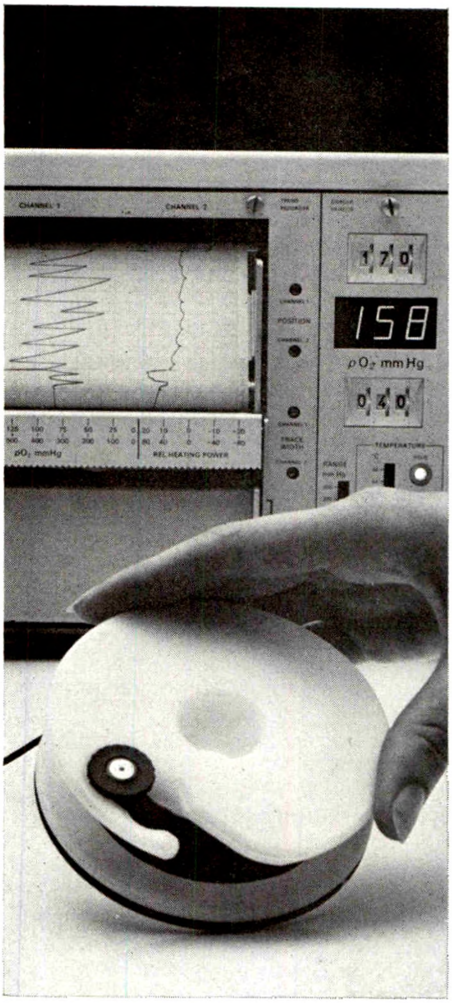

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This investigation was undertaken to establish "normal values" for the zinc, copper, manganese, vanadium, and iodine concentrations of hair in 38 full term neonates.

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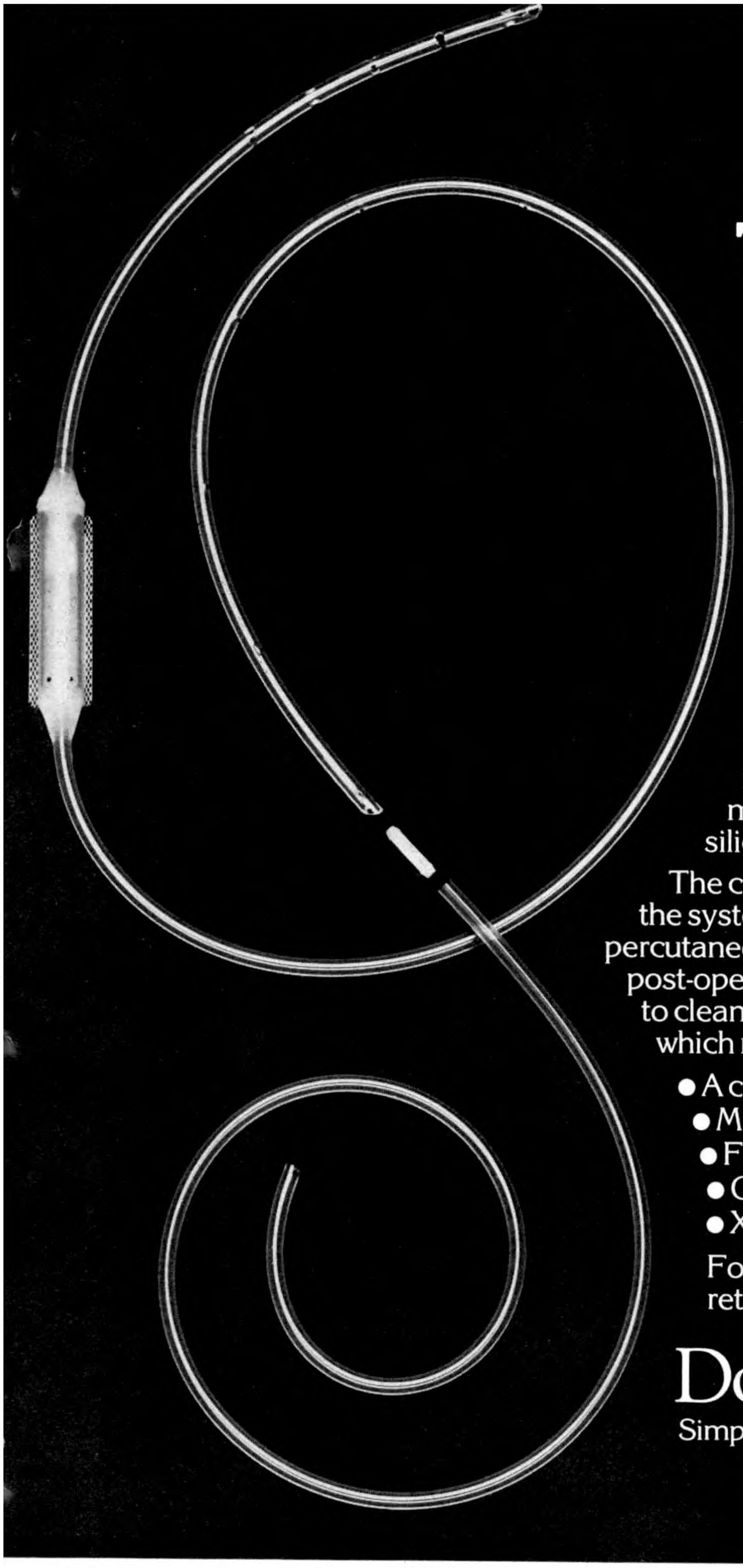

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1. Practical Therapeutics (1975) 10, 112.
2. Postgraduate Medical Journal (1975) 51, 615.

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Archives of Disease in Childhood, 1979, **54**, 813

Editorial

Douglas Gairdner, editor of the *Archives* 1964–79

This special number of the *Archives* is dedicated to Douglas Gairdner by the editors with whom he has worked, the *Archives* staff, the Editorial Committee, and the staff of the *British Medical Journal*.

Since its foundation in 1926, the *Archives* has had 10 editors, who have nearly always worked in pairs. As the list below shows, Douglas Gairdner has been the longest serving, with 16 years in office, followed by Richard Dobbs with 15. Separately and together these two editors have guided the *Archives* for half its life span.

When Douglas joined the *Archives* in 1964 it was published bimonthly. About 180 papers were offered each year and each volume comprised about 600 pages. Publication is now monthly, over 600 papers are received annually, and there are about 1000 pages per volume. The process of scrutiny, refereeing, and editing of papers has become much more exacting for editors and authors alike in the intervening years.

Douglas has been distinguished in many fields—as a clinician, as a research worker of continuing originality over 30 years, and of course as an editor. In 1976 he was awarded the James Spence Medal, the highest award of the British Paediatric Association. In 1978 he received the Dawson Williams Memorial Prize of the British Medical Association for his creative editing of the *Archives*. A brief biographical note, and the lively personal appreciation which Professor Donald Court delivered in presenting the James Spence medal, were published in *Archives* 1977, **52,** 85.

In this issue the personal appreciations refer to Douglas as an editor and friend, and the special annotations are a tribute to the extraordinary breadth and variety of his research interests.

Editors of the *Archives*:

Hugh Thursfield and Reginald Miller, Vols 1–8, 1926–33

Charles Harris and Alan Moncrieff, Vols 9–13, 1934–38

Alan Moncrieff and R. W. B. Ellis, Vols 14–20, 1939–45

R. W. B. Ellis, Vols 21–22, 1946–47

R. W. B. Ellis and P. R. Evans, Vols 23–24, 1948–49

P. R. Evans and I. A. B. Cathie, Vols 25–29, 1950–54

I. A. B. Cathie and Richard Dobbs, Vols 29–38, 1954–63

Richard Dobbs and Douglas Gairdner, Vols 39–44, 1964–69

Douglas Gairdner and Roger Robinson, Vols 44–54, 1969–79

Roger Robinson and Roy Meadow, Vols 55– , 1980– .

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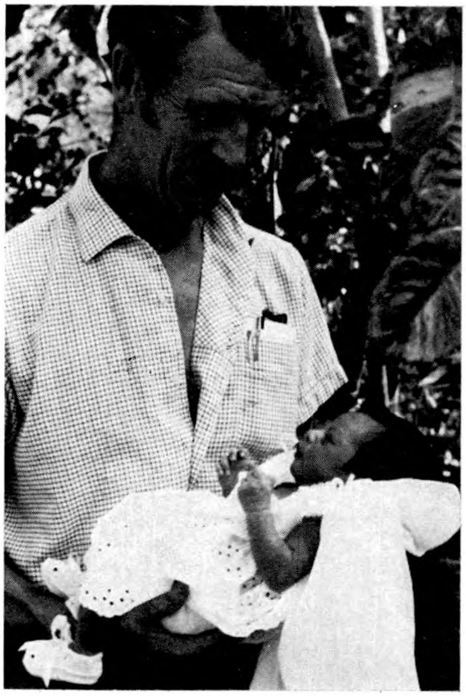

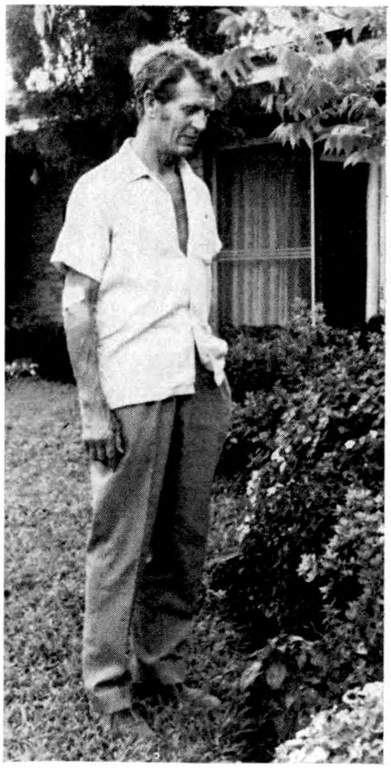

Douglas Gairdner

Archives of Disease in Childhood, 1979, **54**, 815–816

Personal tributes

Douglas as editor

RICHARD DOBBS

Douglas Gairdner joined me as editor of the *Archives of Disease in Childhood* after Ian Cathie resigned in 1964. I nominated Douglas not only because of his medical, paediatric, and literary abilities but also because of his attitude to sailing. Both require an ability to make quick decisions and to take actions which in every sense of the word may have vital consequences. This appreciation of Douglas, at that time one of my crew, and in recent years substantiated when I became one of his crew, arose through his capacity, when faced with an important decision, to ask for opinions, to which he gave careful thought, and then to take decisive action. This, to one who is essentially an impulse sailor, augured well for the important discussions and decisions that need to be taken by the editor of a journal receiving a constant flow of contributions which arrive, like the waves on the sea, out of the blue and which, however light or weighty, need to be carefully assessed.

A newly created journal needs to grow up, and for some years remains a financial burden to its parent organisation. Since its conception in 1926, the *Archives* has been the property of the British Medical Association who financed its birth, infancy, and childhood. During our joint editorship the *Archives* passed through its adolescence, and began to pay its own way. In 1970 discussions began as to whether the British Paediatric Association, which since 1945 had nominated the editors and editorial committee, and to which many of the contributors to the *Archives* belong, should benefit from the profits of the journal. Douglas Gairdner representing the editors of the *Archives*, and I, no longer editor, representing the BPA as its president, remained convinced, paediatrics being not a specialty, but general medicine for a special age group, that the *Archives* and its editorial staff should remain in close association with its elder brother, the BMJ, and the editorial staff continue to benefit from friendly contact with colleagues of all the numerous medical journals housed on the same floor in the same building; and so the journal remained the property of the British Medical Association and the BPA began receiving an annual grant from the profits. During the ensuing years under the editorship of Douglas Gairdner and Roger Robinson the *Archives* has prospered and grown, is now published monthly, and receives increasing contributions from countries outside the British Isles. In 1977, after further discussions between the BPA and the BMA, in which Douglas took a major part, an agreement was signed whereby the two organisations were joint partners in the journal.

An editor of a medical journal not only accepts or rejects papers but himself adds editorial comments, and Douglas has made many notable contributions. Soon after the war he wrote his classical paper on anaphylactoid purpura, which many of us still think of as Gairdner's version of the Henoch and Schönlein condition; and perhaps a more important impact on medical practice, he was one of the first to point out that circumcision is the major one of 3—now 4 or even 5—medically unnecessary operations; this was followed by its gradual elimination, at least as a regular initiation heralding the emergence of the neonate into infancy. Then recently he recounted in the *Archives* an interesting fable regarding a child who survived a 'near fatal' condition, with serious chronic complications, and, who, over six decades later, Douglas assures us is still alive and sufficiently kicking, to be taken on as a sailing crew.

Douglas Gairdner 'retired' from the NHS in 1974 but hasn't noticeably slowed down. In addition to a variety of activities in Cambridge, advising in the local Citizens' Advice Bureau, and playing the tuba in the Royston Brass Band, he has added to his weekly visit to the *Archives* office an outpatient teaching session at the Queen Elizabeth Hospital for Children in the east end. Here, as a senior member of the medical staff commented, the students from the London and St Bartholomew's Hospitals enjoy his shrewd and perceptive medicine, and no one really believes, either from his physical appearance or his teaching style, that he has yet reached retiring age. His colleagues in the editorial office have lively memories of his scarlet-lined waistcoats, his curly blond hair under a yachting cap, and his endearing but maddening habit of leaving his scarf, gloves, brief-case, etc., on trains between Cambridge and London. It is abundantly clear that both he and his wife, Nancy, an enthusiastic physiotherapist, will remain fully involved in life's activities for many years to come.

Archives of Disease in Childhood, 1979, **54**, 817–819

Douglas as editor

ROGER ROBINSON

When I was invited to meet Douglas in 1968 to discuss the possibility that I might join him as editor of the *Archives*, I felt that I was being privileged to meet one of the great names of British paediatrics. As a student, two of the books which had most kindled my interest in paediatrics were the splendid first and second editions of *Recent Advances in Paediatrics*, in which he was both editor and an important contributor. I had also met his name on several important papers—on Schönlein-Henoch syndrome, and on haematology of the newborn. Douglas's constant additions to paediatric knowledge from his own research over the whole of his career remain one of the most remarkable and impressive characteristics of this remarkably impressive man. It must be comparatively unusual to be able to base a number in tribute to a great editor on his own contributions to the literature, but I had no doubt that this was most appropriate for Douglas. My only problem was trying to find all his papers! They have been published in many journals, though he has been very faithful to the *Archives* both before and during his editorship. When I was going through the indices of the *Archives* to locate his contributions since 1948, I started by taking down from the shelves those volumes in which his name appeared. However, it soon became apparent that it was much simpler to take down the volumes in which his name did *not* appear and leave on the shelves the much larger number where it did.

Working with Douglas proved as great a privilege as I had expected, but also full of unexpected pleasures. The alternate Tuesday afternoons of our regular meetings were always occasions to look forward to, and if we had time to meet for lunch beforehand I would be entertained with his conversation which always included sailing but also ranged over archaeology, history, biography, or politics. Douglas is an avid reader of considerable erudition, and would often be bursting with enthusiasm about the book that he had just read on one of these subjects. Human motivation fascinates him, and he would certainly have made a splendid novelist if he had had time to follow five careers instead of just the three or four which he successfully encompassed. What he said was always enlivened by a great sense of humour and by great kindness, something of which I am particularly reminded on looking back over the letters he wrote during our years together as editor.

Whether or not we had a leisurely start to our afternoon's editing, there was always a great deal to discuss and do, and the pace of work and of Douglas's activities would accelerate from about 4.15 pm onwards. At 5 o'clock he would leap up, shoving an armful of papers into a capacious travelling bag (which he regarded as a *sine qua non* for an editor, ordinary brief cases being much too exiguous) and dash out of the office in the curious slightly squashed blue headgear which he called a yachting cap, but which was certainly not Cowes style. One or two things would usually have been left behind, but even in his 70th year his time for the sprint from BMA house to King's Cross would be difficult to beat. Astonishingly, he practically never missed a train.

Douglas's scientific and clinical achievements and his rounded personality have been acclaimed in Donald Court's James Spence medal citation and in the other articles in this special number. I therefore wish to write particularly about his work as editor. Of all the qualities which he brought to this task, the two which impressed me most have been his enthusiasm and conscientiousness. Editing a major journal for 16 years is very hard work. Richard Dobbs compares an editor to the skipper of a yacht, but in some ways I think the editor is more like one of a rowing crew—in the case of the *Archives*, which has a long tradition of two editors working harmoniously together, a coxed pair, the technical editor being the cox. Most editing is a long, steady, hard pull over very similar stretches of water and it is only occasionally that some kind of tidal wave in the shape of angry would-be authors, delays at the printers, or terrible editorial oversights threatens to engulf the boat. New papers come into the office daily—now over 600 a year—and each one is likely to be seen and worked over by the editor several times between its submission and rejection or publication. Every stage on every paper would be dealt with by Douglas with the same scrupulous care.

The popular notion of editors is that they come in two main kinds. On the one hand are policymaking editors, taking a broad view of what the journal should be doing and not too much concerned with details. On the other hand are editorial editors concerned with details of accuracy, style, spelling, and format. If these two kinds of editors exist, Douglas was emphatically both at the same time. He was constantly concerned with the broad responsibilities of the *Archives*. He felt it part of his job to try to obtain the best papers for the journal by keeping his ear to the ground for what was going on in research and being presented at meetings. Could an original paper be encouraged to come our way, or was there some new topic ready to be dealt with in an Annotation or some other special invited article? He was also concerned with trying to take the *Archives* to parts of the world where it was less widely read, and his new ideas for doing this have been a constant theme in the Minutes of meetings of the Editorial Committee over the last 15 years. The ethics of paediatric research is an issue in which he has taken a particular and long-standing interest. He tried to ensure that articles published in the *Archives* met the highest ethical standards and that children were not exploited or misused for research. However, on this subject like all others his view was a balanced and moderate one, and he has also been keen to ensure that proper and beneficial research is protected and not impeded. Of the three policymaking leading articles on this subject published in the *Archives* in the last 12 years, the most important was undoubtedly the 1973 one (Volume 48, page 751), and this was almost entirely written by Douglas.

Douglas's broad editorial grasp was always apparent when we discussed what to do with a difficult paper. Confronted with a lengthy article, often containing unfamiliar technical detail, and a lengthy and detailed referee's report, he would always cut through the befuddlement which is apt to afflict editors in this situation. He would rapidly pick out the main points which the authors were, or ought to have been, making. He would then ask: Was it scientifically convincing? Was it clearly expounded? Was it important? Confusion rapidly vanished.

However, Douglas was also an editor with an irresistible interest in detail and style. A manuscript which he had read—even one we were most unlikely to publish—would always be covered in corrections made either in pencil or in fine ink (the traditional thick blue pencil never seems to have been part of the editorial equipment in this office). All his alterations, his letters to me, and his drafts of letters to authors would be written out in longhand, not always particularly legibly. (Much of Douglas's writing was certainly done on the train between Cambridge and London, but his writing *always* looked as if it had been done on a bumpy train-ride.)

Douglas was particularly appreciative of the invaluable service given to the *Archives* by its technical editors, and he would certainly be very disappointed if this special number did not include a tribute to the splendid work of Rita Carne, Susan Burkhart, and Jennifer Orton, the three who have assisted us during his editorship. However, Douglas's attention to detail, including punctuation and the use of particular words, occasionally led to one of the very few disagreements between him and them. In general, commas are regarded as the property of the technical editors—at least ordinary, common-or-garden, tactical commas which make sentences easier or more difficult to read. Only the much rarer strategic comma which may totally alter the sense of a sentence is regarded as coming within the purview of the editors. But Douglas could sometimes not resist a wholesale attack on commas of all kinds to the consternation especially of Rita Carne. His desire for stylistic accuracy met its Waterloo over a problem related to drug dosage. 'Milligrams per kilogram per day' is an expression in everyday use in clinical medicine. It is of course scientifically and mathematically incorrect, the correct expression being 'mg kg^{-1} day^{-1}'. However, the latter expression is not only a typographical monstrosity but it bears no relation to the colloquial one in clinical use. Douglas chewed over this problem for several years during his editorship. He could not bear the incorrect 'mg/kg/day'. He toyed with various compromises, finishing up with 'mg/kg per day', mainly I think because it at least indicated that we could see there was a problem. However, I believe he still experiences a mild twinge of pain every time he sees this expression printed.

Another stylistic problem which vexed him was that of sibs and siblings. After consulting various genetic experts (who frankly do not seem to have been terribly clear themselves about the distinction between these words), Douglas concluded that the correct term for 'brothers and sisters' was 'sibs', and that 'siblings' was incorrect because it was a diminutive and referred only to children. In the volumes of the *Archives* spanning several years, therefore, the word 'siblings' does not appear unless inadvertently it escaped Douglas's editorial pen. We subsequently discovered that we were quite wrong. 'Siblings' is the correct term for children having one or both parents in common, and 'sib' is a broader and vaguer term connoting kinship. (Interested readers looking up '-ling' in the *Oxford English Dictionary* will find an explanation of why it is not a diminutive in words of this kind.)

Douglas was not particularly put out by this discovery—his occasional conservatism is always blended with a willingness to change in the light of new evidence, and siblings are now to be found in the pages of the *Archives*.

Another example of Douglas's willingness to change even his most cherished ideas concerns the title of this journal. Periodically there are rumblings in the BPA, the Editorial Committee, or just among interested readers, that our title is old fashioned and carries an air of musty Dickensian attics—which is not the image we try to convey. Douglas was always rather fond of the title and was skilled at marshalling arguments in its defence. The truth was that he would have been perfectly happy to change it if someone suggested a better title, but that exercise is a great deal more difficult than it sounds, and so far no one has.

Working for nearly 11 years with Douglas at the *Archives* has been a high privilege and pleasure. The British Paediatric Association, British paediatrics in general, and the journal itself owe him a great debt for all that he has contributed over so many years. However, I will especially remember Tuesday afternoons sitting with him in a smallish room in BMA house at a smallish table piled with papers. About them, and about everything else, he always has something interesting to say.

Archives of Disease in Childhood, 1979, **54**, 820–821

Douglas in retrospect

DERMOD MacCARTHY

For those readers of the *Archives* who have never met Douglas Gairdner he is a tall, good looking man with a very straight back for his age, who carries his head on his shoulders in a youthful manner. He has a slightly Grecian nose and a forehead that is transversely heavily lined, due to moods of levity rather than gravity, as with the creases round his eyes. His hair which was blond has not turned grey or white in his sixties but brown, and being as thick as ever gives a remarkable impression of youth. But, let me say at once, it is not just an impression for he still is in every way extraordinarily young.

It is difficult to describe a man who, because of his capacity to respond to people of all kinds and his liking for intimacy, may present a different image to each of his many friends. Therefore some personal reminiscences must suffice to give an impression of him in the hope that some people will recognise in them resemblances to their own pictures of Douglas.

A few years ago Douglas, when introducing me to someone, added after my name, 'who is my oldest friend'. That warmed me. I could not have wished for an adjective, as a friend, that I liked better. We were both at Gresham's School, Holt and met there about 54 years ago. I remember him then as a good deal smaller than me, although slightly older. When I met him in later years he had shot up. He told me that a late puberty was the reason for this and he always held that it had been an advantage to have been held back by it from his proper age group and then to put on a sprint to manhood at a mentally maturer age. It was much to be recommended, he said. When we met again at Great Ormond Street in 1939 (he a stepping stone or two ahead on the path to paediatrics) we at once started to compare experiences at that puritan but civilised school. I told him that in class we relied on him to bring the master down as David did Goliath. This he did by being sometimes urchin, sometimes puck, imp, buffoon, or leprechaun, 'getting the wires crossed', and of course translating the Latin prose into absurdities which he then defended with many a pained . . . 'but Sir!'. It was very good to find him again and a friendship developed that at school had only been slight. We shared a house in Chelsea until war was declared in September, a delightful 9 months of cooking experiments, music, intimate talk, and flirting with the 'daily'.

At the start of war we were both posted as 'Blood Transfusion Officers' (in anticipation of massive air raid casualties) to the Royal National Orthopaedic Hospital at Stanmore, where an insoluble residue of children from Great Ormond Street had been bundled down to be in comparative safety and where we were to continue to look after them in our spare time. The house in Chelsea was to be left to its fate. It was good bye to all that. We had hurriedly to pack Douglas's car with all our essential belongings and be off. What was 'essential'? That was a good question. There was an exhilaration in discovering that in fact nothing was. I left a great heap of things on the floor unpacked as mere paraphernalia. When we slammed the door and drove off it was a golden afternoon, with a sky that was soon to be blackened by hundreds of bombers. I noticed that Douglas was smiling. Turning round in my seat I noticed his golf clubs rather vulgarly sticking out of the back window. He liked mock heroics.

'Mock obituaries' was a game Douglas invented. We were young and flippant and made fun of the cliché-ridden obituaries of the *BMJ* of the time, doing our own or each other's as we drove from Chelsea to Great Ormond Street in the morning, or employing extravagant 'obituareese' to clap wings on the backs of our dullest contemporaries or most pompous seniors. There was also the 'back to nature obstetrics' game in which Douglas had designed a mock hospital consisting of caves in which women would be delivered in straw, naked of course, and in order to have and to hold the baby immediately would bite through the cord with their teeth; but just to be on the safe side, would undergo a short course of dental hygiene in the antenatal period. Prophetic perhaps?

In our London days we often discussed music and played flute duets, which to be honest were not a great success. Sometimes we played our gramophone records, particularly Nadia Boulanger's marvellous production of Monteverdi's madrigals, something quite new to us and to many young music lovers at the end of the 'thirties. Once, when talking about Handel's Messiah, Douglas made a remark which I was to remember long afterwards; he said how impressed he was by the power of the words in one of the arias . . . 'A man of sorrow, and acquainted with grief'. Warmth and generosity of response to people whether or not in trouble or in need of sympathy we think of as kindness; but an intenser degree of this we would call love. I remembered that remark of Douglas's when, years later, he and Nancy were indeed acquainted with grief, for he became, not a man of sorrow, but one whose kindness was intensified in this way.

Can one distinguish one paediatrician's feelings towards children, as patients, from another's? Yes, of course; but it may be difficult to express it. Douglas always had, quite unsentimentally, a particularly tender feeling for very young children, a feminine as well as a fatherly concern for them, so spontaneous, so beautiful, so vulnerable. He hated seeing them in hospital and in 1956 he gave a paper to the Royal Society of Medicine entitled 'The decline and fall of hospital paediatrics' .Throughout his 27 years at Cambridge he worked with very few beds and could be acclaimed as the paediatrician who admitted the fewest children to hospital and kept them there for the shortest time. It was not his fault that some people, particularly administrators, in the early years of the NHS interpreted the title, and not the substance of his paper, to mean that paediatrics was a dying speciality and that paediatricians, like the tuberculosis officers, were sawing off the branch they were sitting on. We knew what he meant by 'hospital paediatrics'—the child who, no matter how young. languished from week to week in a hospital ward (which was also a sort of museum), between visits of the big chief.

How can one describe him as a man to work with or do things with? The simile that seems most apt for his relationship with others in work or various pursuits is that of first violin in a quartet. Not the grand soloist or the leader of the orchestra but a gifted dominant player, who at the same time feels and needs the music of the other players. In the pages that follow something of this will be appreciated, but for an example of a pursuit, why not take sailing? It is a great test of friendship, loyalty, and niceness or leanings to selfishness. Douglas in a boat is certainly the first fiddle, but how the quartet plays! My first experience of playing under his bow was in 1939, when he knew rather little about it, if I may say so now when he is a great small-boat mariner. The 'Merrythought' was a small shallow-draught yacht. We were 4 aboard. As we sailed out of a little Essex creek towards the sea she suddenly slowed down, then stopped. Instantly we were ordered overboard to shove her off the mud. Stripped to the waist, that is from below upwards, and with shirt tails floating on the turbid water, we pushed and heaved until away we went, clambering aboard with long black stockings, or tights in one case, which we were ordered to wash off before being allowed in the cockpit. But 40 years later, what expert knowledge of navigation and seamanship he has. Sailing back with him from Galway to Harwich I appreciated the enormous amount of planning and detailed care which must have meant plenty of apposite suggestions from Nancy. Much experience and responsibility were displayed in that voyage out and back, in his 31ft 'Lal', so named after a woman who for him from childhood onwards, had always epitomised everything female and femininely beautiful, even in her nineties. The quartet played *allegretto or allegro con brio* all the way and never was there any of the dreadful heartiness and banter that can take possession of the crew of a yacht at sea. Douglas has twice circumnavigated Scotland and has described it beautifully in the *BMJ.* Now he is returned from crossing the Bay of Biscay this year we shall expect another beautiful clear seascape in words.

It is sad that many readers of the *Archives* or *Recent Advances in Paediatrics,* who do not know and may never know Douglas Gairdner, must make do with such a sketch as this. And must be resigned not to hear one of his brilliant imitations, which his friends are often treated to, in the form of lightning impromptu charades, all over in a moment, leaving his audience and himself in fits of laughter.

Archives of Disease in Childhood, 1979, **54**, 822–824

Special annotations

Schönlein-Henoch syndrome

This characteristic syndrome of skin, gastrointestinal, and joint disorders has fascinated many distinguished physicians. Schönlein[1] in Berlin described the association of arthritis and purpuric rash in 1832 and it was one of his former students, Eduard Henoch,[2] who nearly 40 years later described the association of gastrointestinal symptoms and a similar rash. Professor Henoch was one of the first German physicians to specialise in paediatrics. He maintained his interest in the syndrome throughout his life and, at age 90, shortly before his death he recorded the important association of serious kidney disease.[3] Although Schönlein and Henoch gave their names to its eponymous title it does seem that other distinguished physicians had noticed the condition earlier. There is an excellent description by Heberden in 1801, and another by Willan (1808) in his book on cutaneous diseases.[4, 5] At the turn of the century William Osler devoted many of his later years to study of the condition and his concept of 'anaphylactoid purpura' although confusing in some ways did draw a useful comparison between the systemic reaction of serum sickness and the illness of Schönlein-Henoch syndrome.[5] Douglas Gairdner from 'the Department of Child Health, Kings College, University of Durham' completed a paper on the syndrome in 1947 which was a worthy successor to its illustrious predecessors and in many ways it is still the most detailed and accurate description of the syndrome in the English language. His personal observations were based on only 12 cases, but the scholarship, research, and thoughtfulness with which they were presented makes it a more useful paper than many of its successors. It is a long paper, 30 pages, which is perhaps why he published it in the *Quarterly Journal of Medicine*. It might have received wider paediatric acclaim had it been published elsewhere. The description of the skin lesions is excellent and contains many of the points usually overlooked in subsequent publications, but which nevertheless are important diagnostic features, for instance, the way in which the rash apart from having the well known topographical distribution also has a predilection for areas of pressure, with 'a striking delay of from 12–24 hours . . . the skin creases beneath the sphygmomanometer cuff become outlined on the day *after* a blood pressure reading'. The rash is frequently found in bands on the skin near the top of tight socks or at the waist.[6] Gairdner emphasised the way in which the crops of rash could come and go for a very long time; one child whom he studied was still having crops 2 years after onset. His paper also contained what I think is the first description of the variation of the rash that is seen in young preschool children. They often have a more obviously urticarial rash with big weals which later may become purpuric. Oedema of the scalp and face and the dorsum of the hands and feet is common. The only feature he did not mention and which does cause some confusion is the subcutaneous bleeding that may occur almost anywhere, for instance, bleeding into the eyelids and conjunctiva or bleeding into the scrotum mimicking torsion of the testicle.

Further study of the condition has led to the realisation that a variety of other manifestations can occur with the syndrome; nose bleeds may be severe and there may be bleeding into the calf which simulates a deep vein thrombosis; convulsions, encephalopathy, facial palsy, and chorea occasionally occur.[7]

Gairdner's article drew attention to the spectrum of disease ranging from rheumatic fever through Schönlein-Henoch syndrome to polyarteritis nodosa. At the time his article was written streptococcal infection was common and serious in Britain. It is much less common now and less severe. No longer is the streptococcus the commonest antecedent of Schönlein-Henoch syndrome. A variety of infective agents and occurrences have been linked with the syndrome. They range from specific infecting organisms such as *Mycoplasma pneumoniae*[8] and varicella[9] to food allergens,[10] drugs,[11, 12] insect bites,[13] and exposure to cold.[14] The same syndrome can result from a variety of different provocations. Gairdner's suggestion of a link between polyarteritis nodosa and Schönlein-Henoch syndrome is one with which I agree. Polyarteritis nodosa is extremely rare in childhood but occurs either in the infant or, much later, in the teenage childhood. Schönlein-Henoch syndrome is not seen in infants, is most common in young children, and then becomes uncommon in teenage children and adults. It is almost as if the syndrome occurs in childhood instead of polyarteritis nodosa.

Gairdner said 'No treatment has been proved to have any effect upon the course of the illness'; sadly that remark is still true today.[6] Although there is widespread agreement that corticosteroids can have a beneficial effect on the alimentary symptoms,[15] no drug or course of management has been shown to affect the occurrence or recurrence of the disease or its progression. Gairdner, way ahead of his time, decried the use of bed rest for the condition pointing out that it did not seem to influence the course or the prognosis. (The impact on his readers of this splendid *cri de cœur* must have been lessened somewhat by a striking photograph a few pages later showing 'gross purpuric and necrotic lesions on the buttocks, the curved marks corresponding to the edge of the bed pan'.)

Blood-stained urine in a child with the syndrome was recognised by Heberden in 1801.[4] Gairdner was one of the first to suggest that the renal lesion was the most serious component of the syndrome. Nowadays it is the glomerulonephritis which is almost entirely responsible for the 1–3% mortality rate of Schönlein-Henoch syndrome. Of Gairdner's 12 patients, one died of renal failure and another 2 had chronic renal insufficiency. In recent years much information has been obtained about Schönlein-Henoch nephritis from several large surveys.[15,16,17,18,19,20] The proportion of patients reported to have renal involvement varies between 20 and 100% depending upon the criteria for 'renal involvement'. Raised red cell excretion rates in the urine have been found in all children with the syndrome[19] and an abnormal renal histological picture has been reported in children with Schönlein-Henoch syndrome who had normal urine on routine testing.[21] On routine testing between 30 and 70% will have albuminuria and microscopic haematuria and another 20–30% have macroscopic haematuria. Although the renal illness may be most severe in the early stages of the disease a remarkable degree of recovery is possible. Those who have merely microscopic haematuria are likely to be completely normal 10 years later. The large group who have symptomless haematuria and proteinuria on the whole do well although up to 20% may develop permanent renal damage. The small number of children who have acute nephritic syndrome and a nephrotic syndrome early in the course of the illness are those who have the most serious disease. Up to half of them subsequently develop renal insufficiency, but even for that group nearly half appear in good health with reasonable renal function 10 years later.[22,23] The pathology of the renal lesion is well studied and described but does not as yet shed much light on the aetiology.[7,24] Apart from the diffuse mesangial proliferation with pronounced focal variation that is visible on light microscopy, the outstanding finding is IgA deposition in the glomerular mesangium and also occasionally spread along the basement membrane in severe cases.[25] Its similarity to the immunofluorescent appearance of Berger's disease (clinically one of the varieties of 'recurrent haematuria of childhood') raises the question whether Berger's disease is a type of Schönlein-Henoch syndrome; after all we frequently diagnose the syndrome in the absence of involvement of joints, gut, or kidneys, but we never diagnose it in the absence of skin involvement because that is the pathognomic sign. If we had a reliable test for the syndrome we might be diagnosing it in many children who did not have the characteristic rash. Perhaps IgA deposition in the glomerulus and also in blood vessels of the skin is the most important feature.

Schönlein-Henoch nephritis accounts for about 15% of children who are put on dialysis in Europe because of end-stage renal failure. It is important that either prevention or effective treatment is found. So far there is no evidence that any drug affects the course of the renal lesion although there is a shortage of adequately controlled trials and the results of the trial of cyclophosphamide by the International Study of Kidney Disease in Childhood are awaited with interest.

The prevention and management of Schönlein-Henoch syndrome has not advanced as far as Douglas Gairdner must have hoped when he wrote his important paper in 1947. However, it is worth remembering that Sir William Osler published his most useful contribution on the syndrome after his retirement, and that Henoch who was responsible for clearly defining the renal involvement that accompanied the syndrome published that paper in his 90th year. At that rate I shall expect the definitive paper on the cause and prevention of Schönlein-Henoch syndrome to be written by Douglas Gairdner somewhere around the year 2005, and trust that he will publish it in the *Archives of Disease in Childhood* and not in the *Quarterly Journal of Medicine*.

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Nephrotic syndrome of childhood: malaria therapy reconsidered

In 1952 Gairdner[1] and Byrne[2] independently reported that acute infection with malaria could induce a remission of what was then known as nephrosis or type-II nephritis of Ellis.[3] Gairdner was stimulated to investigate this type of treatment by the long-lasting remissions, amounting to cures, that occasionally followed measles in the nephrotic child[4], and recently he reported 'a notable case of nephrosis' illustrating the duration of this effect.[5]

In his paper in 1952, Gairdner described 4 children with nephrosis infected with *Plasmodium vivax*.[1] The case reports are interesting: 'On 12 January 1949, malarial mosquitoes were applied. . . . On 24 January malarial fever began, the temperature rising to 102°F. Next day diuresis set in and oedema began to subside rapidly, disappearing completely by 2 February'. However, albuminuria persisted, although in another child it cleared completely. The malarial attacks were terminated by mepacrine. One of the 2 children who did not respond developed renal failure and was shown at necropsy to have crescentic nephritis.

Subsequently, Gairdner and Shute collected the clinical details of the 65 children with nephrosis for whom the Malarial Reference Laboratory had supplied infected blood or mosquitoes.[6] 51 of these were considered to be cases of 'pure nephrosis', of whom 14 had a complete remission, although 4 of them subsequently relapsed and another 4 had proteinuria at follow-up. There was one death associated with malaria treatment, and 6 patients required transfusion.

These trials of malaria therapy were naturally not controlled, but nevertheless the impression is gained that in some cases there was a close temporal relationship between malarial fever and remission of the nephrotic syndrome. However, these were the years of excitement after the introduction of corticosteroid treatment for the nephrotic syndrome,[7] and even alkylating agents were looming on the horizon[8] so that a possible therapeutic effect of malaria was not pursued. Malaria therapy is considered in this Annotation in the light of contemporary understanding of the immunopathogenesis of the nephrotic syndrome.

Terminology

The nephrotic syndrome consists of a disturbance of glomerular permeability resulting in albuminuria, hypoalbuminaemia, and oedema. Most children respond to treatment with corticosteroids and have only slight histological changes in the glomeruli evident on light microscopical examination. The condition was called 'lipoid nephrosis' by Munk,[9] but the term nephrosis has been attacked by Oliver[10] as etymologically meaningless, and the adjective lipoid emphasises an aspect of the disease that is of only secondary importance. Some authors refer to the condition as the 'idiopathic nephrotic syndrome', which implies an optimistic assessment of current understanding of the pathogenesis of other forms of the nephrotic syndrome. Recently the term 'minimal-change nephrotic syndrome' has been popular, but there is a certain illogicality, unfortunately common in the nosology of renal disease, in the use of a pathological term to describe a condition essentially recognised by its clinical features; in many cases a renal biopsy will not be undertaken, and the histological appearances will therefore remain a presumption. The expression 'steroid-responsive nephrotic syndrome' (SRNS) at least has the merit of focusing on the most important objective characteristic of the condition, but has the disadvantage of excluding a few otherwise similar cases which do not respond to conventional corticosteroid regimens.[11]

Immunological aspects

The pathogenesis of SRNS is not known, but it is tempting to speculate that immunological mechanisms are involved. However, critical laboratory evidence of immunopathogenesis has not been forthcoming, and in cases where immunological abnormalities are observed, it is often difficult to decide whether they are a secondary effect of the nephrotic state or an epiphenomenon of the event that precipitated the relapse rather than an integral part of the pathogenetic mechanism.

Clinical observations. A number of clinical observations have suggested an immunopathogenesis of SRNS. In the first place, relapses are often precipitated by upper respiratory infections. There is an increased incidence of atopy, particularly infantile eczema or hay fever, which was reported in 38% of the nephrotic children compared with 18% of age-matched controls,[12] and there are some well-documented cases in which relapses of the nephrotic syndrome were associated with atopic features—such as grass pollen hypersensitivity[13, 14, 15] and possibly milk allergy.[16] The condition is more common in children who have the second series tissue antigen HLA-B12.[12] The association with HLA-B12 however is weak, with a relative risk of 6·3, but has been confirmed by a further study.[17] There appears to be an increased incidence of minimal-change nephrotic syndrome in patients with Hodgkin's disease, but in only 5 of the 35 reported cases has the condition been demonstrated to respond to corticosteroids alone.[18]

Pathology. About 80% of nephrotic children referred to specialist centres respond to treatment with corticosteroids[19, 20]; of these 93% have minimal histological changes of the glomeruli evident on light microscopical examination and the others have mild mesangial proliferative lesions or focal glomerulosclerosis, although the histological frontiers of 'minimal-change' are difficult to define. 5% of children with minimal-change histology do not respond to treatment with corticosteroids, although in some of these deep focal sclerotic lesions may have been missed in superficial biopsies.

Immunofluorescence studies do not show glomerular deposition of immunoglobulins or complement components.[21, 22] However, immunofluorescent methods may not be sufficiently sensitive, and it is possible experimentally to produce fatal immune complex glomerulonephritis without detectable glomerular deposition of immunoglobulin.[23] An early report that IgE could be detected in the glomeruli of nephrotic patients[24] has not been confirmed in other studies.[25, 26]

The actual site of the filtration barrier in the glomerulus which excludes proteins of the size of albumin from the glomerular filtrate is probably the split-pore diaphragm between the epithelial foot processes[27] which has a complex electron microscopical ultrastructure in which glomerular polyanions containing sialic acid residues play an integral role.[28] Electron microscopical examination generally shows fusion of epithelial foot processes in SRNS,[29] but as similar lesions can be induced in dogs by plasma infusions sufficient to cause proteinuria,[30] and as foot-process fusion persists for several weeks after remission of proteinuria,[31] it is considered that this abnormality is a consequence rather than the cause of proteinuria. Interestingly, both the aminonucleoside puromycin[32] and polycations[33] cause foot-process fusion, and Brenner and coworkers have speculated that the primary event in the nephrotic syndrome is a loss of the glomerular polyanion structure resulting in a diminished restriction of filtration of circulating polyanions, and thus albuminuria, as well as a disturbance of the foot-process structure with fusion.[34] In this context, the report of a 6-fold increase in serum-free polyamines in nephrotic children is of interest.[35]

Immunoglobulins. The plasma concentrations of IgG, IgA, and IgM are normal in remission, but IgG and IgA decrease during relapse and IgM rises.[36] It has been suggested that IgM levels remain high in remission,[37, 38] but these observations probably result from allowing insufficient time for the effects of the previous relapse to wear off. Plasma IgE is raised in one-quarter of nephrotic children, independent of the state of relapse or remission,[12, 39, 40] and there are also raised levels of IgE antibody to Timothy grass pollen and *Dermatophagoides pteronyssinus.*

Complement. Total haemolytic complement is normal in these patients[21, 41] as is plasma C3,[42] and there is no immunoelectrophoretic evidence of C3 conversion *in vivo.*[43] Plasma C4 and Clq levels are generally found to be normal,[36, 38] although there was an earlier report of reduced plasma Clq in some patients.[44] The low plasma factor B concentration is due to urinary loss,[36] and has been considered responsible for defective opsonisation of *Escherichia coli* by nephrotic sera.[45] C3b inactivator (KAF) levels are reduced as well.[46] Immunoconglutinin (IK), an autoantibody to hidden antigenic determinants in C3 and C4 is detectable in nephrotic sera during relapse, suggesting complement activation,[41] but Mallick found a less consistent relationship between IK peaks and relapse in nephrotic patients.[38] Smith and co-workers reported that sera from SRNS children in relapse inhibited the formation of EAC-rosettes by normal human tonsillar B-lymphocytes, suggesting the presence of free or complexed C3b.[47] Taken together, the IK and EAC-rosette data suggest low grade activation of the complement system.

Immune complexes. Recently Levinsky and coworkers reported the detection of circulating immune complexes in the sera of nephrotic children in relapse by a technique dependent on the inhibition of agglutination of IgG-coated latex particles by rabbit IgM antibody to human IgG.[48] Complexes were detected in relapse and persisted for several weeks after remission; they were thought not to be an artefact of nephrotic sera as they were not detectable in congenital nephrotic patients. The complexes were of moderate size (molecular weight 2–2·5 $\times 10^6$ daltons), and interestingly did not bind Clq, suggesting that if there is complement activation, it involves the alternative pathway. Immune complexes were not however detected in the sera of minimal-change nephrotic patients by a Raji cell radioimmunoassay or by a radiolabelled Clq binding assay,[49] but it is not at all unexpected for the various methods of immune complex testing to give differing results.

Lymphocytes. The absolute number of circulating T-lymphocytes, recognised by sheep erythrocyte rosette formation, is normal in nephrotic patients, as are the numbers of the subpopulations of T-cells which bind IgM or IgG, although IgG-binding cells increase in response to corticosteroids.[50] The response of SRNS lymphocytes to phytohaemagglutinin (PHA) is poor,[51] and the response to the T-cell mitogen concanavallin-A is more depressed than the response to PHA (S. N. Chapman and G. Williams, 1979, personal communication). Moorthy and co-workers demonstrated that nephrotic sera inhibited ^{3}H-thymidine uptake by normal lymphocytes in response to PHA or allogeneic mitomycin-treated lymphocytes.[52] However these lymphocyte systems are susceptible to nonspecific influences such as anaesthesia.[53] Ooi and co-workers described lymphocytotoxins in minimal-change nephrotic sera, but in many other diseases as well.[54] Leucocyte migration inhibition by nephrotic lymphocytes exposed to a crude antigen from neonatal human kidney cortex has been demonstrated,[55] but sensitisation to glomerular basement membrane antigens is generally not detectable.[56] Eyres and co-workers have also reported that lymphocytotoxicity for epithelial cells cultured from neonatal human renal cortex is specifically associated with the minimal-change nephrotic syndrome.[57] However, lymphocytes are not evident histologically in the kidneys of nephrotic patients, and therefore it is difficult to imagine that such observations are relevant to the pathogenesis of the disorder. Lagrue and co-workers described lymphokine activity in the supernatant of nephrotic lymphocyte cultures which increased vascular permeability on intradermal injection in a guinea-pig, and proteinuria on injection into the renal artery of a rat. They presented pharmacological evidence suggesting that the lymphokine stimulated the kinin system,[58, 59, 60] and there is some evidence that the kinin system is indeed activated in nephrotic patients.[61] However, we[62] have not been able to detect the differences in vascular permeability factor between nephrotic patients and controls as reported by Lagrue and co-workers.[58, 59, 60] The data so far presented on lymphocyte function in the nephrotic syndrome are intriguing but do not yet present a coherent picture; Shalhoub's suggestion that the syndrome results from a disorder of T-cell function remains speculative.[63]

Treatment

Corticosteroids. Corticosteroid treatment of childhood nephrotic syndrome was introduced nearly 30 years ago but has not been established by controlled trial.[7] The Medical Research Council conducted a trial in adult nephrotic patients, in which it was noted that there was a trend towards a higher mortality in the prednisone-treated group compared with controls; in patients with minimal change histology the disappearance of proteinuria was more rapid on treatment, but among the controls the proteinuria had nevertheless fallen to <1 g/24 h in more than half the patients 2 years after entry into the trial.[64] The same tendency to natural recovery was evident in nephrotic children before the advent of corticosteroids.[65] However, the risks of the nephrotic state are such that it would not be justified to withhold corticosteroids for any significant length of time from a nephrotic child, and the effect of corticosteroid treatment in inducing remission is obvious enough for a controlled trial not to be now necessary or appropriate. There is, however, an appreciable need for controlled trials to evaluate different methods of administration of corticosteroids, and many of the recommendations are a normal adrenal response in maintaining remislogists differ.[66]

Two-thirds of the responders will relapse. Leisti and co-workers reported an association between early relapse and a poor cortisol response to ACTH after the first course of corticosteroids, and have demonstrated that 7·5–15 mg daily of prophylactic cortisol prevents relapse, emphasising the role of a normal adrenal response in maintaining remission.[67, 68]

Immunosuppressives. It is paradoxical that the major role of immunosuppressive agents in the treatment of the nephrotic syndrome of childhood is in that group with the least convincing evidence of immunopathogenesis—that is the corticosteroid-responders and the minimal change corticosteroid-resistant patients. Alkylating agents were first used in 1952[8] and the first report of the use of cyclophosphamide appeared 16 years ago.[69] It is well established that cyclophosphamide can prevent relapse of the corticosteroid-responsive nephrotic syndrome.[70, 71] An 8-week course of cyclophosphamide in a dosage of 3 mg/kg per 24 hours results in about 75% of patients remaining in remission for one year and 50% for 5 years.[72] Results are better in older children, but children with HLA-B12 do not fare so well.[12, 17] There is no benefit to be gained from longer courses or higher doses, but shorter courses are less effective.[73, 74, 75] Cyclophosphamide is an immuno-

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suppressive drug acting principally on B-cells,[76] but there is no rigorous evidence to support the general assumption that its effect in SRNS is mediated by its immunosuppressive properties. Chlorambucil in a dosage rising to 0·3 mg/kg per 24 hours is as effective as cyclophosphamide in inducing a sustained remission.[77] Azathioprine is not effective in preventing relapse.[78, 79]

Malaria. In the light of this rather fragmentary evidence on the pathogenesis of SRNS, how can we view the possible effect of malaria described by Gairdner? The first explanation to be considered is that malarial fever, like measles, stimulates the pituitary-adrenal axis, and that the remissions are a consequence of this. However, this is not a very satisfying explanation: why should some infections induce remission, while others, particularly viral upper respiratory infections, characteristically precipitate a relapse?

The interaction between malaria and the immune system is complex.[80] There are the immunological consequences or side effects of the acute infection, for example, the immune-complex deposition responsible for the nephrotic syndrome in African children infected with *Plasmodium malariae*.[81] However, of greater relevance is the immunosuppressive effect of malaria. Children infected with *Plasmodium falciparum* have a diminished response to the O antigen of *Salmonella typhi*, to tetanus toxoid, and to meningococcal vaccine, but have normal cellular immune responses.[82, 83] The immune response of BALB/c mice to type-III pneumococcal polysaccharide is abolished by infection with the murine *Plasmodium yoelii*,[84] and the antibody response to sheep red cells is blunted by *Plasmodium bergei* infection without detectable effect on cellular immune responses.[85] The mechanism of this immune paresis is still a matter for discussion and may involve macrophage function, but it seems that malaria, like cyclophosphamide, has a more profound effect on B-cell than on T-cell function. It is of considerable interest that both *P. bergei* infection[86] and cyclophosphamide[87] ameliorate the nephritis accompanying the autoimmune disease of New Zealand black/white F_1 hybrid mice.

The effect of measles on the immune system is however different, and, as with corticosteroids, there is a more profound effect on T-cell function, reflected in the observation of Von Pirquet who first described depression of the tuberculin response during acute measles infection.[88] Although the theoretical immunologist would have no difficulty in constructing several hypotheses to encompass the described phenomena, we sadly agree, 25 years later, with Gairdner: 'it is tempting to speculate further on the mechanism of malaria-induced remissions; but, in view of our fundamental ignorance of the cause of nephrosis, such speculations would be nugatory'.[6]

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Blood formation in infancy

It is hard to believe that 27 years have passed since the first of Douglas Gairdner's papers on this subject was published in the *Archives*.[1] Although he was later to write about other aspects of neonatal haematology—such as the postnatal plasma shift[2, 3] and the control of acidosis during exchange transfusion[4]—it is perhaps his 4 papers about red cell formation[1, 5, 6, 7] which have best stood the test of time and are still 'required references' (on both sides of the Atlantic) in any article about the physiological anaemia of the newborn or the anaemia of prematurity.

In the first paper[1] the authors described the appearance of the bone marrow in normal infants during the first 3 months of life. Each baby was selected from those whose mother, having already had a normal baby, had volunteered to take part in the project. The examination of the marrow showed a decline in erythroid activity during the first one to 2 months which paralleled the fall in haemoglobin and was accompanied by a pronounced increase in marrow lymphocytes, a finding which could be misinterpreted by the unwary observer as true red cell hypoplasia. We still do not know if these 'lymphocytes' so prominent in the marrow at the nadir of erythroid activity are all truly lymphoid cells; some of them perhaps, residing in the null (non-T, non-B) fraction are stem cells or early erythroid precursors awaiting a surge of erythropoietin to nudge them into differentiation and multiplication.

In the next two papers[5, 6] results of measurement of haemoglobin, red cell count, PCV, and reticulocytes during the first 3 months on the same group of normal term babies and in a large number of cord blood samples were reported. The relative macrocytosis of neonatal red cells, the low reticulocyte count, and the progressive decline in haemoglobin between 2 and 9 weeks were noted. The authors were not the first to make these measurements, but they related them to the changing bone marrow appearances to produce a classical description of the pattern of normal neonatal erythropoiesis. The advent of the electronic counter has made more accurate red cells counts and direct measurement of the MCV possible and the use of these techniques confirms the pattern of red cell values during the first months after birth.[8, 9] Gairdner and his colleagues attributed the changing red cell picture after birth to decreased red cell production and to the effect of body growth rather than to accelerated red cell destruction. They concluded that in the fetus and the infant, erythropoiesis was governed by the arterial oxyhaemoglobin level and that erythropoietic activity was regulated to ensure a level in the fetus and newborn of about 11 g of oxyhaemoglobin per 100 ml blood.

How do these conclusions look a quarter of a century later? It has been shown, using ^{51}Cr-labelled autologous red cells that the fall in haemoglobin is due to an actual decrease in red cell mass rather than to expansion of plasma volume.[10] The red cell of the term baby, examined in the isotope era, has a life span of about two-thirds of the adult cell;[11] that this is due to an intrinsic defect has been shown by infusion of DF^{32P}*-labelled neonatal cells into normal adults.[12] There are now substantial descriptions about the metabolic characteristics of the fetal erythrocyte which include greater glucose consumption, reduced phosphofructokinase, and increased levels of other glycolytic enzymes and greater susceptibility to oxidant injury.[13] However no relationship has been established between these metabolic abnormalities, which are not simply those of a young red cell population, and the cells' relatively short survival. In the last months of fetal life the estimated rate of red cell production is 3 to 5 times that of adult life[14] and it has been suggested that this intense erythroid activity results in formation of short-lived macrocytes, so-called stress reticulocytes.[15]

Despite this evidence of decreased red cell survival, the major factor in the postnatal decline of haemoglobin is, as Gairdner surmised, decreased red cell production. The decline in marrow erythroid activity is reflected in decreased ^{59}Fe clearance and incorporation into red cells.[16] It is now evident that red cell production is mediated through the effect of tissue oxygen tension on the output of the hormone erythropoietin.[17] The site of erythropoietin production remains controversial. Although in postnatal life it is probably the kidney, fetal erythropoietin, the production of which is independent of the mother, may be made in the liver. The main effect of erythropoietin is to stimulate committed erythroid precursor cells to differentiate to proerythroblasts.[18] Erythropoietin can be detected in the plasma of the fetus and in cord blood from the newborn infant, but levels decline rapidly after birth until between 8 and 12 weeks when its reappearance heralds the resumption of erythroid activity in the bone marrow.[19, 20] Anaemic and hypoxic infants continue to produce erythropoietin during the first weeks after birth and, as Gairdner observed, show no decline in marrow activity.

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*DF^{32P} = di-isopropyl phosphofluoridate.

The postnatal decline in erythropoietin production and the subsequent fall in haemoglobin is therefore a physiological response to the rise in arterial oxygen saturation at birth and the resulting increase in oxygen delivery to the tissues. More slowly the left shifted haemoglobin-oxygen dissociation curve which, in the fetus, favours transfer of oxygen from the maternal to the fetal circulation, gradually shifts to the right, favouring increased oxygen delivery to the tissues without impairment of oxygen loading in the lungs. This shift of the curve is mediated by the presence of increasing amounts of adult haemoglobin with increased binding of the phosphate ester 2,3 diphosphoglycerate (23DPG). It has been calculated that at a mixed venous O_2 tension of 40 mmHg the 3-month-old infant delivers more oxygen to his tissues than a neonate despite a fall in Hb from 17·0 to 10·5 g/dl.[21]

The replacement of fetal by adult haemoglobin is a function of fetal maturity and is uninfluenced by the timing of birth. Haemoglobin A is synthesised in small amounts (5–10%) from 6 to 8 weeks' gestation, until 32–36 weeks when there is a sharp increase in the synthesis of Hb A and a decline in that of Hb F; the switch is not confined to one cell line making Hb A alone and is not restricted to either marrow or hepatic erythropoiesis.[22] The mechanism of the 'switch' remains unknown, tantalisingly, since ability to reverse the process might provide an effective treatment of disorders of β-thalassaemia and sickle cell anaemia by endowing permanent possession of 100% haemoglobin F. Homozygous hereditary persistence of fetal haemoglobin and possession of haemoglobin variants with high oxygen affinity both appear compatible with normal growth and health despite possession of a permanently left-shifted haemoglobin-oxygen dissociation curve.[23]

What of the earlier and more profound drop in haemoglobin which occurs in the preterm infant? Gairdner and his colleagues distinguished between this *early* anaemia of prematurity occurring between the 2nd and 4th months after birth and the *late* anaemia occurring after 5 to 6 months; the latter being clearly due to iron deficiency. They next addressed the problem of the early anaemia.[7] Their attention, like that of many others, was partly diverted by haematinic red herrings. Cobalt, now known to stimulate production of erythropoietin, was given to 5 premature babies and caused reticulocytosis and a rise in haemoglobin but was unacceptably toxic resulting in transient exopthalmos and goitre.

Gairdner also investigated the use of oral iron and found that giving it from the 3rd week mitigated but did not prevent the early anaemia of prematurity. It has since been shown that this anaemia is not associated with a low serum iron or raised TIBC and is not influenced by early administration of oral iron.[24] Iron stores in the preterm infant are influenced by birthweight and blood loss (particularly iatrogenic), and by feeding practices; iron is readily absorbed from breast milk and breast-fed infants attain greater iron stores than those fed artificially.[25, 26] Nevertheless the preterm baby fed on breast milk, like the artificially-fed premature baby, is at risk of developing a late anaemia due to iron deficiency unless he receives additional iron. A recent prospective study of low birthweight infants used sequential measurements of Hb, iron, and TIBC and also serum ferritin, the most sensitive index of tissue iron stores. One half of the babies received supplementary iron. The same nadir of haemoglobin was reached at 2 months in both groups; by 3 months iron stores were significantly lower in the control group and by 6 months most babies in the control group, whether breast or bottle fed, were iron deficient and anaemic.[27]

The problem of iron supplementation was compounded for a while by the vitamin E story. 12 years ago it was reported that a group of low birthweight infants developed haemolytic anaemia, thrombocytosis, and oedema associated with decreased plasma levels of vitamin E and increased sensitivity of the red cells to peroxide haemolysis.[28] A number of similar reports followed and it seemed possible that vitamin E deficiency might play a role in the anaemia of prematurity. However it is now apparent that this haemolytic anaemia is a result of highly unphysiological dietary manipulation. The lipid content of the red cell membrane reflects the lipid content of the diet and in low birthweight preterm babies fed certain proprietary milks rich in polyunsaturated fatty acids the membrane becomes a substrate at risk of peroxidation. Plasma vitamin E (antioxidant) levels are low in such babies and the addition of iron generates free radicals which initiate the process of peroxide haemolysis of the red cell membrane.[29, 30, 31] Thus the haemolytic anaemia is a multifactorial disorder of artificially-fed low birthweight premature infants receiving early iron supplements: it is therefore preventable.

Serum and red-cell folate levels are relatively high in the newborn but may fall in the preterm infant within a few weeks to levels which are low by adult standards. Despite this, megaloblastic anaemia is extremely rare and there is no evidence that folate supplementation influences the early anaemia of prematurity. It has been suggested that folate supplements should be given to very immature babies or to those who are at risk of dietary deficiency.[32] Breast feeding should obviate this risk, since plasma and red-cell folate levels in breast-fed infants are higher than in adult controls.[33] It seems therefore, that breast milk is best haematinically as in every other respect.

The early anaemia of prematurity now known to be uninfluenced by haematinics, often exacerbated by venepuncture, is, like that of the mature baby, associated with reticulocytopenia and decreased marrow activity.[7, 34] Erythropoietin, measured by bioassay, was detected in the urine of premature infants at birth but was then undetected until the haemoglobin declined to a nadir at 5 to 7 weeks. Hypoxic premature infants continued to produce erythropoietin.[35] It is claimed that radioimmunoassay is a more sensitive technique for measuring erythropoietin than bioassay, but the reliability of immunoassay is at present controversial. Erythropoietin was detected using radioimmunoassay in low concentration in the plasma of premature infants. There was a significant inverse correlation between plasma erythropoietin and haemoglobin and an even more significant inverse correlation between erythropoietin and oxygen-unloading capacity of the blood. This is hardly surprising since measurement of oxygen-unloading capacity takes account not only of the haemoglobin but also of the position of the haemoglobin-oxygen dissociation curve both of which affect oxygen delivery to the tissues. In infants with right shifted curves (that is, those who had been transfused and had relatively large amounts of adult haemoglobin) the haemoglobin fell lower before an erythropoietin response was observed.[36] These results suggest that premature infants respond appropriately to a decrease in oxygen-unloading capacity by increased erythropoietin excretion.

The reason for the earlier fall in haemoglobin in the premature baby is not entirely clear. One possible factor may be decreased red cell survival; the scanty data available suggest that red cell survival in the preterm baby is shorter than in the mature infant.[11]

Stockman and Oski have recently reviewed the present state of knowledge of the anaemia of the newborn, much of it derived from their own work. They suggest that low oxygen consumption in the preterm baby allows a more profound drop in haemoglobin before reactivation of erythropoiesis, and consider that the 'anaemia' of prematurity is compatible with adequate tissue oxygenation.[37] However, most recent work on oxygen consumption indicates that O_2 consumption is higher in the preterm baby[38, 39] than in more mature infants.

The assumption that anaemia in the preterm newborn is physiological has been challenged in a recent paper in the *Archives* in which are reported results of measurement of haemoglobin, reticulocytes, P50 (partial pressure of oxygen at which Hb is 50% saturated), and available-oxygen. The figure for 'available-oxygen' is derived from the haemoglobin concentration and P50, and is calculated to be the amount of oxygen capable of being released per dl of blood. These values were correlated with the clinical features at the nadir of the anaemia. In babies of 33 weeks' gestation the clinical features of anaemia appeared to correlate better with available oxygen than with haemoglobin or P50 values; surprisingly this correlation did not hold for more mature babies, even those of 33–34 weeks' gestation. In some babies with relatively high haemoglobin but low available oxygen who were judged clinically anaemic, symptoms of anaemia improved after transfusion.[40]

The clinical features of anaemia are as nonspecific in the infant as in the adult, but it is difficult to define a more objective way of assessing them. Simple comparisons of 'available-oxygen' in the preterm baby and the adult do not allow for the fact that cardiac output is much higher in the newborn infant than in the adult.

For the moment, rather than embarking on a policy of liberal transfusion with all its attendant dangers, we should continue to observe the generally accepted criteria[41] while trying to determine more precisely which babies may benefit from transfusion.

It is good that the *Archives*, under Douglas Gairdner's editorship, has continued to provide a forum for debate about blood formation in infancy. To argue whether anaemia is 'physiological' or not is surely a question of semantics. Recent research has at least reminded us of the importance of concentrating not only on oxygen uptake and arterial oxygenation, but also on oxygen unloading at the tissues.

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Aetiology of hyaline membrane disease

The demonstration that the lungs from infants with hyaline membrane disease (HMD) have abnormal surface properties[1] sparked off a decade of intensive study on the structure and mechanical aspects of the lungs in this condition. Douglas Gairdner played a major role in a series of classical papers on the subject which virtually brought this era to a close. The first paper gave a detailed comparison of the different methods which can be used to evaluate the surface properties of the lung in the perinatal period.[2] The others described the cellular structure and lecithin content of the lungs from perinatal deaths, particularly from babies dying with HMD.[3, 4]

This work clearly established the sequence of structural and functional events in the lungs of infants with HMD associated with surfactant deficiency. The earliest change was shown to be an interstitial oedema with localised necrosis and desquamation of alveolar epithelial cells and absence of osmiophilic granules in the type II cells. Progressive development of hyaline membranes and the initiation of repair phenomena with return of osmiophilic granules and normal surface properties were described in detail. It was recognised that hyaline membranes could develop in some cases despite normal lung surfactant and that lack of surfactant occurs, though rarely, in the term infant. In conjunction with quantitative estimates of lung lecithin content, this provided a formidable amount of new information which complemented and amplified the work published during the preceding decade.

Changing directions in HMD research

Since that time the directions of research into the perinatal lung and HMD have altered in response to two major advances. The first of these was the demonstration by Liggins that prenatal glucocorticoid administration to fetal lambs allowed them to survive if born prematurely.[5] This has prompted widespread research into the pharmacology and endocrinology of fetal lung maturation. The use of prenatal corticosteroid administration to mature the preterm infant lung *in utero*, thus preventing the development of HMD, was subsequently introduced,[6] although relative benefits and hazards are still the subjects of arguments.[7] The second major advance was the discovery by Gluck and co-workers that infants at risk of developing HMD could be detected prenatally by measurement of lecithin/sphingomyelin ratios in fluid obtained by amniocentesis.[8] The twin possibilities of being able to diagnose and treat surfactant deficiency before birth have not unnaturally preoccupied medical research workers to the exclusion of the more fundamental questions about how and why the condition arises in particular circumstances.

In this, as in other fields of medical research, real advances are episodic and each one provokes a flurry of subsidiary activity centred on the particular area of the problem highlighted by the initial work, rather than on attempts to integrate it with all other aspects of the problem. It is justifiable to ask whether we are any closer to understanding the aetiology of HMD than we were 10 years ago.

Control of fetal lung development

The problem of the aetiology of HMD is of course just a part of the far wider problem of control of fetal lung development in general. The mammalian fetal lung develops as a hollow fluid-filled organ that must be capable of rapid transformation into an efficient air-filled gas-exchange system within minutes of birth. The human lung differs from that of other mammalian species in the ability to perform this feat at any time in the last trimester of pregnancy.

Recent work on the rabbit indicates that normal mammalian fetal lung growth requires the integration of neuromuscular and secretory activities.[9] Secretion of lung liquid appears to provide a moulding force for the developing lobule which is probably enhanced by the swings in intrathoracic pressure associated with fetal respiratory movements. There is evidence that agents such as corticosteroids which cause premature structural and biochemical maturation of the lungs may also retard their growth.[10] Diversion of substrate to surfactant production could well reduce the quantity available for cell proliferation. There may therefore be a biological advantage in the lung remaining functionally immature, provided that biochemical maturation can rapidly be induced when delivery becomes imminent. To allow efficient transition to an air-breathing state one might postulate the presence of one or more early warning systems to trigger biochemical lung maturation at the onset of labour.[11] HMD would then arise as a result of failure to activate these systems or the inability of the target tissue to respond.

Trigger mechanisms for biochemical lung maturation

It is well established that endogenous glucocorticoid production is capable of inducing the enzymes necessary for surfactant synthesis[12] and specific cortisol receptors have been demonstrated in the fetal lung.[13] The glucocorticoid mechanism may adequately explain the advanced lung maturation seen in various forms of fetal stress including infection[14] or recurrent antepartum haemorrhage.[15] Although most animal species have a surge in cortisol production near the end of pregnancy it is not yet clear how important this mechanism is for normal human fetal lung maturation.[12] Infants with congenital absence of the adrenals or anencephaly[16] may be born with lungs which show normal surface properties. It is also unclear how much of the wide variation in lung maturity at any gestational age[3, 17] can be accounted for by the variable activation of this mechanism. Are there specific pathways for triggering lung maturation by methods other than cortisol release?

There is evidence that thyroxine can promote lung maturation[18] as can pharmacological agents such as pilocarpine.[19] An additional, possibly important, pathway is the autonomic nervous system.[20] Infusion of catecholamines in lambs causes inhibition of lung liquid secretion and release of surfactant.[21, 22] It is not yet established whether surfactant synthesis is increased but it would be intellectually satisfying to have a link between removal of lung liquid and enhanced surfactant production since these would be sensible activities for the fetal lung when faced with imminent discharge into a gaseous environment.

Prolonged rupture of the membranes is associated with advanced lung maturation in the human.[23, 24] This may provide a nonspecific stress which induces lung maturation directly by the glucocorticoid mechanism, or such stress might be the result of secondary infection of the liquor. It is interesting to speculate whether the intimate relationship between the fetal airways and the amniotic fluid may allow triggering of some more direct mechanism for biochemical lung maturation after rupture of the amniotic sac.

Conclusions

The main structural and functional features of HMD associated with surfactant deficiency have been well understood for a number of years.

The problem of aetiology which remains to be resolved is what determines that a particular infant develops this condition of apparent immaturity, while another infant of considerably lower maturity does not.

It is suggested that the solution of this problem demands greater understanding of the way that the fetal respiratory system interacts with its environment and of the mechanisms which influence the balance between growth and biochemical maturation of the fetal lung.

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Management of hyaline membrane disease

In 1962, Arshad Warley and Douglas Gairdner wrote 'Management of the condition must at present rest on (1) recognition of the physiological disturbances present in the individual case; and (2) correction of these disturbances, so far as this may be possible, in order that the baby can be given optimal conditions for survival during . . . a self-limited illness'.[1]

17 years later this statement still summarises perfectly the neonatologist's role in producing neurologically intact survivors from hyaline membrane disease (HMD). The great advances made in recent years in understanding the role and effect of surfacant deficiency in HMD show how both these maxims still apply in the management of the condition. The avoidance of acidaemia, hypothermia, prematurity, and overventilation of the lung, each of which diminishes lung surfacant, is of prime importance in the management of such babies today.

The management of HMD can be considered under three headings. (1) The control, and if possible the normalisation, of the blood–gases. (2) The control, and if possible the normalisation, of the biochemical and physiological abnormalities generally seen in any group of seriously ill patients in intensive care—for example, hypotension, hypothermia, electrolyte imbalances, oliguria, paralytic ileus. (3) The prevention if possible, but otherwise the control of the side effects both of the treatment and the disease—for example, patent ductus arteriosus (PDA) and bronchopulmonary dysplasia.

Control of blood–gases

At the beginning of the 1960s three important studies combined to improve the treatment for infants with HMD. Firstly, Avery and Oppenheimer,[2] in the USA, suggested that the restriction of inspired oxygen concentration to <40% in an attempt to prevent retrolental fibroplasia (RLF) resulted in a higher mortality from HMD. Cross[3] and Bolton[4] subsequently gave identical data for the UK.

Secondly, Strang and McLeish[5] and Warley and Gairdner[1] showed that the primary defect in oxygenation in HMD was due to right-to-left shunting, and not, among other things, to diffusion difficulties through the hyaline membranes, aptly described as 'eosinophilic red herrings' by Gruenwald.[6]

Thirdly, Ashton[7] showed that it was the oxygen in the blood supplying the retina, rather than the oxygen in contact with the cornea, which caused RLF.

Those paediatricians, in whose view it had always been ridiculous to restrict infants to 40% oxygen, irrespective of cyanosis and progressive vascular collapse, were therefore encouraged to go on administering sufficient oxygen to keep the baby pink and, as arterial blood–gas analysis became available, to keep his Pa_{O_2} in the normal range of 60–90 mmHg (7·98–11·97 kPa).

It was shown that it was possible safely and efficiently to monitor the Pa_{O_2} on blood drawn from an umbilical arterial catheter, without the risk of RLF, and to keep it in this range, while the baby was breathing oxygen concentrations >40% for prolonged periods of time.[8]

The management of oxygenation in babies with HMD is therefore to increase the inspired oxygen concentration enough to keep the arterial Pa_{O_2} 60–90 mmHg. Would that this was all we had to do to keep the Pa_{O_2} normal!

One-third of all babies with HMD so treated in 1968 were still dying. The main reason for death was progressive hypoxaemia and respiratory failure, and the neurological sequelae—such as intraventricular haemorrhage (IVH).[8] Better ways of oxygenating infants were needed and soon were to be provided.

It had long been apparent that breathing was hard work for infants with HMD, and that some way of helping them should be devised. In 1953, Love and Tillery[9] attempted to keep the baby's lungs expanded by attaching a towel clip around the xiphisternum and suspending it from the incubator roof by means of an elastic band. Warley and Gairdner[1] used a variation of this by suspending a weight from a stitch placed under the xiphisternum. Uncontrolled, and uncomfortable, these attempts at what was really continuous positive airways pressure (CPAP) did not achieve clinical acclaim. Yet the report of Gregory and co-workers[10] applying CPAP by endotracheal tube and head box ushered in a new mode of respiratory support for infants with HMD.

Many ways of applying CPAP have been tried but most neonatologists now prefer to use either a closely fitting face mask or nasal prongs, and only apply CPAP via an endotracheal tube when weaning the baby off intermittent positive pressure ventilation (IPPV). Head boxes and bags, and negative pressure chambers have generally been abandoned because they seriously restrict access to the baby and setting them up involves the excessive handling of the frail, ill infant.

No new technique in the treatment of HMD has so thoroughly been researched and evaluated as CPAP. There can be no doubt that it raises the Pao_2 in infants with HMD, but does this benefit the baby, or does it merely give the physician that inner glow of satisfaction that comes from achieving biochemical normality? Four controlled trials have shown slight benefit, measured in terms of survival, but this was usually restricted to infants weighing >1·5 kg[11,12,13,14] no doubt due to the fact that in these units the techniques for giving IPPV were so refined that most babies with HMD would have survived regardless of what treatment was given before receiving artificial ventilation.

More germane perhaps is whether CPAP improves the infant's chances in other ways. Theoretically it should; it improves oxygenation, makes respiration more regular,[15] and it lessens surfacant consumption.[16] Durbin and co-workers[13] showed that infants receiving CPAP before IPPV were easier to ventilate. Other studies confirmed that postponing the use of CPAP until HMD was severe, and 70–80% oxygen was required to keep blood-gases normal, resulted in a more prolonged illness that was more likely to progress to the need for IPPV.[17,18,19] However these studies, as was the case with the ones on survival, also showed there was little benefit from giving early CPAP in infants <1·5 kg, although we now think that these are the very infants who benefit most. Currently we give such infants low pressure CPAP (2–4 cmH_2O) by nasal prong if they show any sign of HMD or if they require increased inspired oxygen concentrations in the first 4–6 hours of life. In larger babies we still keep to the general rule of starting CPAP when >60% oxygen is required to keep the Pao_2 >60 mmHg.[20]

The use of CPAP can lead to complications, but these are primarily associated with the use of endotracheal tubes or devices with a tight neck seal.[21] When CPAP is applied by means of a mask or prong, the main risk is pneumothorax with an incidence of 20% in some reports. Furthermore one-third of infants requiring CPAP progress to the need for IPPV, and this figure increases to nearly 60% for infants <1·5 kg.[22] For these reasons CPAP should only be used in neonatal units where high standards of intensive care exist.

In such units there can be no doubt that CPAP has contributed significantly to the survival of infants with HMD, and while it is clearly not a panacea,[23] one can only endorse the view of Chernick[24] 'One or two controlled trials in the use of constant distending pressure in severe HMD, although daring, are welcome; many more would be foolish'.

The medical profession has recently acquired a needless obsession for changing their habits only when convinced by random controlled trials.[25] Fortunately CPAP was generally accepted before the rather dismal results of such trials were published. Few would suggest a need for a trial of IPPV in patients who were apnoeic or merely gasping; to do so would be as ludicrous as a trial of external cardiac massage in cardiac arrest! Yet trials have been done and the cynical reader will not be surprised to find that IPPV only helps particular groups of infants—the smaller ones,[26] the bigger ones,[27] or none![28] In fairness to these studies it should be noted that often ventilators were being used which were less than ideal, and that IPPV was started *before* apnoea and gasping intervened. In North America many infants are still ventilated on the indication of abnormal blood-gas values, but in Britain, influenced by Reynolds,[29] ventilation is rarely started on the basis of poor blood-gases alone.

Much research has gone into how best to ventilate infants with HMD. Reynolds[30] has summarised the current views that most infants on ventilators are optimally oxygenated at rates of 30–40/min with inspiratory:expiratory ratios of about 2:1 and using about 5 cm of positive end expiratory pressure (PEEP). If these guidelines are used, peak inflating pressures exceeding 30 cmH_2O are rarely needed.

The fact that 75–80% of infants >1·0 kg with HMD who are ventilated because they are apnoeic now survive is surely a vindication (irrespective of random controlled trials) of Donald and Lord's vision in 1953,[31] the same year that Love and Tillery[9] were suspending babies from incubator roofs with elastic bands, that some form of artificial ventilation would enormously improve the chances of survival for these infants.

With CPAP or IPPV it is generally possible to keep most infants with HMD oxygenated. If this fails two other techniques have been advocated. Two reports showed a better survival rate in low birthweight infants with HMD after exchange transfusion with fresh adult blood which increased the P50 of the infant's blood.[32,33] However this has not been confirmed by others,[34] and so the technique has not generally been used. More recently the use of intravenous or intra-arterial tolazoline was shown to improve Pao_2 in infants with severe hypoxaemia from RDS.[35]

Comparatively little attention has been given to the control of CO_2, although as long ago as 1961 it was suggested that this might be a factor in the genesis of IVH.[5] Other than when weaning infants off IPPV it is unusual, in my experience, to see $Paco_2$ values >80 mmHg (>10·64 kPa), and it has long been my practice to ignore CO_2 retention if the other blood–gases are satisfactory, particularly in infants with chronic lung disease. However, the neonatal brain blood flow does increase with increased $Paco_2$,[36] and if this is combined with loss, after asphyxia, of autoregulation of cerebral blood flow to changes in blood pressure[37] it is easy to see how the coexistence of hypercapnia, asphyxia, and pronounced changes in blood pressure, which is not uncommon in HMD, could predispose to IVH. In the future perhaps more attention will be paid to keeping the CO_2 under control.

While comparatively little has been written about controlling respiratory acidosis, much has been written about controlling metabolic acidaemia. Four facts need to be remembered when discussing intravenous base therapy in the newborn. (1) With birth asphyxia, the administration of base expedites the onset of breathing and lessens the risk of brain damage.[38,39] (2) The heart works less well when bathed in acid,[40] and the fall in cardiac output thus induced has many secondary effects. (3) Surfacant synthesis turns off at pH <7·25.[41] (4) Metabolic acidaemia after the first hour of life can be lessened if not stopped by meticulous attention to maintenance of blood volume, oxygenation, and renal function.

Infusing alkali can be harmful. THAM causes apnoea,[42] while bicarbonate causes alarming surges in osmolality and blood volume,[43] and if infused to excess may induce IVH.[44] However rational use of base has not been associated with IVH.[45, 46, 47, 48] The studies implicating bicarbonate treatment in the genesis of IVH have never adequately tackled the possibility that sicker babies, more prone to surges in cerebral blood flow through damaged capillaries, are more likely to have received bicarbonate. Other studies merely confuse the issue—for example by combining IVH with other types of intracranial haemorrhage, such as subdurals which clearly have a different aetiology,[49] or by stating that it is pointless giving bicarbonate in a closed system such as RDS.[50] Clearly it is not.[43]

Routine infusions or bolus injections of base to *all* infants at risk from, or suffering from, mild degrees of acidaemia have been shown to be of no benefit in random controlled trials. Indeed one would hardly expect them to be.[47,51,52,53] There is much information on when, how, and to whom base should not be given. This must be heeded, but it should not detract from the use of bicarbonate in babies with acidaemia >5–10 mmol/l. Since Usher's first study[54] it has been apparent that administration of bicarbonate given at rates <1 mmol/min to carefully selected babies who are acidaemic improves their chances of survival.[55,56]

Control of other physiological abnormalities

Temperature. It has been known since the studies of Blackfan and Yaglou[57] that maintenance of the infant's body temperature was an important component of keeping him alive, and the extensive studies by Hey[58] gave us the basic information needed to keep his core temperature normal. In infants hypoxic with HMD, who are therefore unable to sustain their body temperatures by brown fat metabolism,[59] it is extremely important to regulate the environmental temperature, as surfacant synthesis and function are compromised if the body temperature falls below 35°C.[60,61]

Haematocrit (packed cell volume) and blood pressure. Infants with HMD are more hypotensive and have lower packed cell volumes than unaffected infants, and particularly low values are found in fatal cases.[62,63,64,65] There is no evidence from controlled trials that transfusion to correct anaemia or hypotension, or both, increases the chance of survival, but there is a plethora of clinical experience showing that hypotensive anaemic neonates improve (assessed by improved tissue perfusion and a rising Pao_2) when transfusion is given. Indeed, I always feel embarrassed when discussing the transfusion habits of neonatologists with other physicians as they become slightly patronising when told that we require evidence from controlled trials to justify transfusing a patient who has symptoms of hypovolaemia and a blood pressure half normal.

On the basis of the study of Robinson and co-workers[66] it would seem reasonable to transfuse sick neonates until a systolic blood pressure of about 35 mmHg is attained. Haematocrit values in excess of 40% should also be sustained. This is particularly true for babies being given IPPV plus PEEP for whom the maintenance of an adequate blood volume is essential.[67]

Infection. No one can like the concept of prophylactic antibiotics less than I do. Yet the mortality associated with unrecognised and virtually unrecognisable group B streptococcal sepsis masquerading as HMD immediately after birth is imposing the need to give all dyspnoeic infants a course of benzyl pencillin for at least 48 hours until cultures are known to be negative, unless some clearly noninfectious condition, like pneumothorax or congenital malformation, is responsible for the dyspnoea.[68,69]

Analysis of our data shows that 90% of infants were given antibiotics, either before or shortly after IPPV was begun[22] usually because it was not possible to exclude infection as being the cause for the deterioration which had necessitated the introduction of IPPV.

Feeding. We have I believe, become obsessed with getting food into babies to the point of it becoming harmful. Sick infants have an ileus[70] and it is therefore most unlikely that orally-administered milk will be absorbed. Unpublished analysis of our data showed this to be true. Furthermore feeding causes apnoea and reduces the Pa_{O_2}.[71] It also obstructs the nostrils[72] and can introduce germs into the bowel by way of the nasogastric tube.[73] For all these reasons infants with HMD requiring more than 40-50% oxygen or ventilatory assistance should not be fed, nor should they have nasogastric tubes passed for the first 24 to 48 hours. However the very small sick infant will have low caloric reserves that will sustain him for only a few days. For 3 or 4 days he can be given intravenous glucose electrolyte solutions, by which time even if he is on a ventilator having initially been very ill he may show signs of bowel activity—bowel sounds or meconium passage. In such infants, and those recovering from HMD, a nasogastric tube can be passed and milk feeding started, but checks should always be made to ensure that the milk is not pooling in the stomach. In infants who are recovering, oral feeding usually proceeds satisfactorily, but some infants still on IPPV will not tolerate oral feeding, and intravenous feeding should then be begun.

Monitoring. Improved monitoring of the infant during his illness has contributed to the rising survival rate in infants with HMD. Regular blood-gas analysis was established over a decade ago,[8] but within the last few years the use of continuous Pa_{O_2} catheters has stressed the fact that even 3- or 4-hourly sampling of blood-gases gives very poor information about the swings and variations in the infant's oxygenation.[74] Continuous Pa_{O_2} monitoring should now be part of the care for all infants with HMD. Furthermore since access to the arterial tree is required for blood pressure monitoring, pH and Pa_{O_2} analysis, and for biochemical and haematological measurements, I believe that arterial catheterisation remains the procedure of choice for blood-gas monitoring in sick neonates despite the promising results of transcutaneous P_{O_2} monitoring.[75] Although frequent complications of umbilical artery catheters continue to be reported from the USA this is at complete variance with my own experience both currently and in the past.[76]

The presence of an indwelling arterial catheter enables one to monitor the neonate's oxygen and BP continuously, Pa_{CO_2}, pH, and PCV 3 or 4 times a day, and electrolytes and calcium daily or twice daily as indicated, without breaking that most crucial law of neonatal intensive care—minimal handling. Furthermore the use of continuous Pa_{O_2} catheters has reinforced this law since catheters show the large and potentially damaging falls in Pa_{O_2} which follow even minor interventions.[77] Additionally, ECG and inspired oxygen concentrations should be monitored continuously and some form of apnoea monitoring device must be used, all in ways that give the maximum of information with the least interference to the baby.

The nursing staff by their constant observation and care of the infant, aided by the electronic devices, should be able to detect any minor deterioration in the infant's condition in time for prompt and efficient correction.

Treatment of side effects and associated disorders. With these standards of care the mortality rate from HMD is now about 10%[78] but new problems have appeared. The incidence of PDA[79,80] and necrotising enterocolitis (NEC)[81] in infants with HMD has become a serious matter in the USA although they seem to be less common in the UK. Is there perhaps some factor that links this with their high incidence of umbilical artery occlusions? Certainly, gut hypoperfusion—perhaps induced by an indwelling catheter—is a factor in the aetiology of NEC, and excessive fluid through a catheter may cause PDA.[82]

However out of adversity, some good does come, since the treatment of PDA with prostaglandin synthetase inhibitors[80] must count among the most exciting developments of the decade in neonatal cardiology.

Bronchopulmonary dysplasia (BPD) is a persisting problem on both sides of the Atlantic. Although this was initially attributed to oxygen toxicity[83] this explanation has always seemed naive, as the striking feature identifying cases of BPD was that such babies had received high pressure positive pressure ventilation, and babies have breathed high oxygen concentrations for prolonged periods of time in the past without developing this disease. Reynolds and Taghizadeh[84] showed that in infants with HMD, ventilation designed to lessen the applied pressures reduced the chance of the condition, irrespective of the oxygen concentration, and Stocks and Godfrey[85] showed that persisting abnormalities of respiratory mechanics on such infants are more a function of IPPV than of oxygen therapy. BPD may be minimised by early use of CPAP to lessen the pressures necessary should IPPV subsequently be required.[13]

Conclusion

It is a platitude that prevention is better than cure. Nevertheless it must be said that despite these great improvements in neonatal intensive care it behoves paediatricians to strive to ensure that fewer babies will need to benefit from them.

With better socioeconomic conditions and a higher standard of both general education and antenatal tuition, it is to be hoped that premature labour producing infants at risk from HMD will not only become a rarity but, if it should occur, will be recognised by the mother early enough for newer and more effective tocolytic agents to be administered. These will either prevent delivery or delay it long enough for effective and safe drugs to be used as surfacant inducers, rather than the corticosteroids, heroin, or aminophylline used at present. For the neonate, so lost to all sense of medical decency and decorum to be born without adequate pulmonary surfacant it may soon be possible to give him some.[86]

HMD will become rare but the techniques of management to which Douglas Gairdner and his department in Cambridge contributed so much during the last 20 years, must not be forgotten so that small sick babies with this and other conditions will continue to benefit from high standards of neonatal intensive care.

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Fat in the newborn

In 1972 I received the improbable message that Douglas Gairdner wanted my advice. Our only previous contact had been on editorial matters, with me in the supplicant role, although I must nearly have met him in a different supplicant role while I waited for his niece to emerge from 19 Adams Road in March 1959. But it was far from clear to me what a research fellow had to offer him. Nevertheless, the request was pursued, he really did seem to want to see me and, what was more, it was the mountain that was going to do the moving.

Eventually he arrived at the Institute of Child Health bursting with the youthful vigour most of us never had, brandishing an Ogden's tobacco tin full of stubby little needles, a sight odd enough for any narcotic investigator. It was these that were the cause of his problem because his latest research interest, which had to do with body fat, was being frustrated by his inability to obtain samples of adipose tissue from little babies through these fine needles. Being the man he is, he had sought help from the literature and may well be the only reader of my MD thesis in the Cambridge University library. At all events I was able to give him some of my 3-inch FG 12 Bell and Croyden specials and, needless to say, he never looked back.

Between 1975 and 1977 Douglas published 3 papers on body fat in infancy.[1,2,3] The first and the last, respectively on the composition of body fat in infants and on the assessment of total body fat, were incidental to the most important of this triad, which was entitled 'Size of adipose cells in infancy'. At the time the number of infants that had been studied was extremely small. Data were available on older children, but information on the earliest and perhaps most important part of the adipose cell size and number story was lacking. Douglas's contribution focused on cell size, which is what one actually observes and measures, and that, as will be seen, was a seminal influence.

Natural history of adipose cell development

Fat cells become recognisable in the human fetus only in the last trimester of pregnancy but there are few data on cell size in preterm infants and Douglas's are probably the best. At between 25 and 30 weeks of gestation the mean adipose cell diameter is between 30 and 50 μm and this increases to 50 to 80 μm by term[2]. Site-to-site differences were apparent from the earliest time of sampling and gluteal samples regularly contained bigger fat cells than samples taken from the abdominal wall. This discrepancy increases as children get bigger so that the site from which adipose cells are taken is of considerable importance.[4]

During the first year of life adipose cell diameter continues to increase and by one year of age gluteal fat cells are about 100 μm in diameter.[5] As Douglas presciently remarked in a 'strictly tentative conclusion', the increase in body fat in the first year of life seems to be largely accounted for by a 5-fold increase in adipose cell volume.[6] Fat cell number does not change during this time in normal children and fat cell size does not change afterwards, so that by 18 months the gluteal fat cell diameter is the same as in normal adults.[7] It is now generally agreed that growth of body fat in normal persons is accommodated by increases in the size of fat cells during infancy and by increases in their numbers afterwards.

While it has been known for some time that fat cells once acquired cannot be lost, the idea that new fat cells can be formed at any time is a relatively new one[8,9] but one which is becoming increasingly clear.[10] The fact that really huge fat cells are not found in the very obese adult strongly suggests that there is a maximum fat cell size, and that when this size is reached, adipose cell replication begins.[11] The postulated critical size could change with age but the concept of size being the trigger to cell replication rather nicely explains the observations made on adipose cell numbers in normal infants described above and in pathological situations later in childhood and adult life.[12]

Changes in skinfold thickness and body fat with age

Many authors have been intrigued by the rapidity of the increase in skinfold thicknesses in infancy because it is so odd that suddenly at one year of age they stop increasing and indeed decrease in normal subjects. Surprisingly, it was not until 1973 that some data became available in England[13] which were incorporated into standard charts,[14] although Sweden was well ahead in this field.[15] Values at birth[16] are of little value as an indication of maturity,[17] but the description of their increase is now fairly well established for our population. It is worth pointing out that what applies in one country may not necessarily apply elsewhere; the pattern is quite different in Berlin, for example,[18] and comparisons can be made only with great caution.

As an isolated measurement, skinfold thickness is of limited value, but to translate skinfold measurements into terms of total body fat is a useful exercise clinically. This has been done in adults[19] and now that accurate methods for determining body fat are becoming available there are indications that skinfold thicknesses more accurately measure body fat in adults than do measures of body density.[20] In children the methodological problems of densitometry are considerable: heavy water[21] and ^{40}K[7] have been used as references for the calculation of lean body mass against which to compare skinfold thicknesses, but neither method is very satisfactory because there is so little evidence about the water and potassium content of the lean body mass in children.

In infants, whom we knew to be wetter, extrapolation from childhood values may give very dubious results, so Dauncey *et al.* used a geometrical method of calculating body fatness in infants.[3] Their formula stands up well to refined techniques of measuring body fatness, such as using xenon.[22] For practical purposes we can assume that a combination of skinfold thickness measurements gives a good indication of body fatness in infants[23] and I do not think that any serious study on nutrition in children in 1979 can afford to omit the measurement of skinfold thickness. Weight and weight-for-height indices are indirect measurements of nutritional status and are unreliable as indicators of body fatness in children[24,25] and adults.[20,26,27] We would be better without them.

Determinants of body fatness in infancy

Knowledge about the determinants of fatness is sparse both in children and adults. One of the classical ways of looking at genetic and environmental contributions to the determination of a characteristic is to compare monozygotic with dizygotic twins, but it seems likely that in body fatness this model has served us badly. Studies of both normal[28] and obese[29] twins have suggested a strong genetic contribution to body fatness, but placing reliability upon differences between twins depends on monozygotic and dizygotic twins being treated alike. If like-twins are treated more alike just because they look alike, a spuriously high correlation will be generated between them and the reverse could apply to dizygotic twins. There is evidence to suggest that identical twin pairs share more environmental factors in common than non-identical twins.[30,31] This has almost certainly affected the calculations on determinants of body fat. Hawk and Brook showed that siblings resemble each other hardly at all, while monozygotic twins resemble each other closely, and dizygotic twins are intermediate.[32] Neither we, nor Mueller and Titcombe found midparent-offspring correlations to be higher than individual parent-offspring correlations, which one would certainly expect in a genetically-determined characteristic.[33] At the time of writing the balance of evidence suggests that body fatness is largely determined by environmental factors.

These data are extremely hard to obtain and are not yet available for infants. The fact that fatter mothers have fatter babies[34] would fit with any theory of determination of body fatness and I am inclined to think that what Hawk and Brook showed for adults is likely to apply in infancy.[32]

Implications

With body fatness contributing significantly to the major risk factors for arteriosclerosis (hypertension, reduced glucose tolerance, carbohydrate induced hyperlipidaemia, lack of exercise), although it is not now itself considered a risk factor,[35] much interest has arisen about whether body fatness tracks. Do fat babies stay fat? Are the seeds of adult fatness sown in childhood?

It has been difficult to answer such questions, not least because people will weigh babies rather than measure how fat they are. This is bound to cause problems, since weight is mainly determined by height and overfeeding before weaning increases height.[36] I accept that babies whose weights reach the 90th centile during the first 6 months may have an increased risk of obesity later[37] and that famine in infancy may 'protect' against obesity,[38] but to argue from these huge retrospective studies that weight gain in infancy is the major determinant of body fatness in childhood is not supported by the facts obtained from measurements of skinfold thickness.[39] Nor do our recent data suggest that body fatness tracks reliably into adult life either for individuals of normal fatness or for those whose skinfold thicknesses in childhood were above the 75th centile.[40]

It is important to note that a number of skinfolds need to be measured to express opinions about changes in body fatness over a number of years, because fat distribution changes markedly with advancing age as the Table shows. A combination of skinfold thicknesses gives the best indication of body fatness[19] and the least between-observer error.[41,42]

Our family data support the idea that body fatness is largely environmentally determined at all

Table *Percentage increases in skinfold thickness with age (6–70 years)*

	Males	*Females*
Triceps	50	150
Biceps	25	66
Subscapular	250	233
Suprailiac	400	220

Data from Hawk (1978).[31]

ages and our longitudinal data suggest that some individuals carry with them into adult life the habits of their childhood, while others, left to their own devices, do not.

Conclusion

Body fat appears in infants through the accumulation of fat in already existing fat cells. Overfeeding causes fat cell hypertrophy which is probably the trigger for fat cell replication at any time of life. Some periods of rapid change could be more sensitive in this respect than others. Once formed, fat cells persist, but neither their size nor their number has been shown to determine levels of fatness. Fatness in adults and children appears to be largely environmentally determined. Evidence that childhood skinfold thicknesses predict well from values in infancy or adult values from childhood ones is lacking. Obesity is bad for adults and children, but greatness cannot be said to be thrust upon them.

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Know the normal, or else . . .

Most babies are born in working order, and Douglas Gairdner,[1] writing about the not so private part of the new boy, in his classical and famous paper entitled 'The fate of the foreskin', described the normal separation of the foreskin from the glans, the age at which the separation normally occurs, and the undesirability of trying forcibly to retract the foreskin, at least in the first 3 years. But there are still many doctors and nurses who tell mothers that they must try to pull the foreskin back, causing pain while risking the development of paraphimosis, and clinic doctors who describe 'the redundant foreskin' or a 'pinhole meatus'. There are still many doctors who, not knowing the normal, cause defenceless boys to be circumcised. Douglas Gairdner mentioned the meatal ulcer as one of the untoward results of circumcision: Denis Browne added many others seen by him—such as urethral fistula and strange cosmetic results.[2] Now Annunziato and Goldblum add the staphylococcal scalded skin syndrome,[3] and Sussman *et al.* the Fournier's syndrome of gangrene of the genitalia.[4]

Miller *et al.* drew attention to another 'sequel' by the 4th birthday; boys who had been circumcised were at least 7 times more likely to have their tonsils removed than were the uncircumcised.[5] The Defence Organisations in Britain recently had to pay £18 000 in settlement for a circumcision which led to gangrene of the tip of the penis: and in the USA, where a higher price is placed on the organ, a settlement of approximately $3 million had to be made for a similar disaster. Kaplan in his 33-page review, having remarked that circumcision is the most common operation on males in USA, and that the cost of newborn circumcision there is calculated at $59 544 000 a year, devoted 16 pages to complications of the operation.[6]

Morgan, probably taking his cue from Douglas Gairdner, wrote two papers on the subject of circumcision—'The rape of the phallus', and 'Penile plunder', again emphasising some consequences of not knowing the normal.[7, 8]

Children can suffer much harm at the hands of doctors who do not know the normal, and the normal variations which do not require treatment. One has seen young babies operated on for tongue tie, or cysts of the gum or palate, which disappear if left alone. One sees older infants operated on for a lipoma in the sole of the foot, for which treatment is unnecessary. Although watering of the eye resulting from incomplete opening of the nasolacrimal duct almost always cures itself without probing, there are still some who attempt this. Müller *et al.* showed that the bends in the lower part of the tear duct make it impossible for a probe to penetrate Hasner's membrane so that probing inevitably produces a false passage; they recommend syringing if anything has to be done, but they state that the duct can open spontaneously as late as the 2nd year.[9] Probing requires a general anaesthetic, and I know of a death which resulted. One hears of operations for toeing in, toeing out, curly toes, flat feet, knock knee, or bow legs, and in none is treatment generally required.[10, 11] A physician's ignorance of the normal plays into the hands of over-active surgeons.

When Mueler inspected the tonsils of 640 children aged 5 to 16 and reported that only 14% had 'normal' tonsils,[12] one wonders how the word normal should be defined. Denzer and Felshin described a study in New York in which tonsils of 1000 11-year-old children were investigated: 610 of children were found to have had the tonsils removed, and when the remaining 390 were referred to ENT specialists, all but 65 of them were advised to have the tonsils removed because they were 'abnormal'.[13]

The observation of a click in the hip of the newborn causes innumerable babies to be placed in 'double nappies', despite the current opinion that the 'click' is of no significance and that double nappies are a useless form of treatment.[14] According to Ramsey, Ortolani wrote that the important 'clunk' or 'jerk' is never found under age 3 months, an opinion with which Ramsey agreed.

One has seen many incorrect diagnoses of cerebral palsy because of failure to recognise normal variations in muscle tone, in the briskness of tendon jerks, or in motor development. This can be a tragedy for the child: I have seen a normal child rejected for adoption on the grounds that he was spastic. I am convinced that only an expert should be allowed to cause a child's adoption to be rejected on the grounds of some abnormality. One has seen children subjected to prolonged physiotherapy at enormous inconvenience to the parents and expense to the NHS for supposed cerebral palsy, when in fact there was no abnormality.

A bizarre feature of paediatrics in some quarters is the widespread application of the terms 'brain-damaged', or 'minimal brain dysfunction' (or 'damage'), or the 'hyperkinetic syndrome', to children whose behaviour disturbs adults. Schmitt wrote that over 100 symptoms have been put into this ragbag diagnosis.[15] Rutter,[16] and Sandberg *et al.*[17] showed that there is no justification for designating these symptoms a 'syndrome'. There is much to be said for making a diagnosis which no one can prove or disprove, as long as it does no harm. Doctors feel better when they have put a name to a condition, whether or not the name means anything, but the term 'brain damaged' is harmful to the child because it 'labels' him, with the risk that teachers will treat him differently from others, with the self-fulfilling prophecy effect. In certain countries these labelled children are given daily stimulant pills with side effects which include stunting of growth, while the child is started on the pill-taking pill-dependent track which may affect him for life. Furthermore, parents are greatly distressed when told that their child is 'brain-damaged'. No one can deny that an occasional child is truly 'overactive': but the diagnosis of the hyperkinetic syndrome, or slight brain damage, is often applied to normal children who have got nothing wrong with them (and need no treatment for taking after one or other of their parents). Many do not realise that there is no psychological or other test which proves that a child's symptoms are due to brain-damage.

Failure to know what is normal, or a mere normal variation not requiring treatment, may cause serious parental anxiety in many other ways. I have seen numerous normal children who had been said to be mentally defective, spastic, or hydrocephalic. I have seen mothers who were told that their normal babies were spastic because they were 'not showing the right responses', or had a 'persistent primitive reflex'. The mother of a 6-month-old baby was told by a health visitor that her child's head was 'too small'. The health visitor had failed to relate the size of the head to the size of the baby and, in fact, the baby was normal with an unusually high developmental quotient. A health visitor stated that she 'failed' 40% of babies at the 6-month assessment, and I found that she had told the mothers that their babies had failed. On the Continent I heard that at the 8-month assessment babies were being referred in considerable numbers to psychiatrists, psychologists, neurologists and others, and that in the 4-year-old assessment 40% were thought to be retarded. Many are insensitive to the psychological implications of referrals from assessment clinics: referrals for suspected defects of vision, hearing, or the hips are usually essential, but apart from those, referrals may cause much parental anxiety without any advantage to the child. Many referrals are due to failure to recognise the range of normality, often because of reliance on charts showing the centile distribution of milestones of development or physical growth. In fact one can never draw the line between normal and abnormal, and the fact that a child's milestone, weight or height, is below a certain centile by no means proves that he is abnormal. Centile charts should be used with judgement. Unless a doctor uses clinical judgement and knows the normal and normal variations, many normal children will be subjected to unnecessary investigations which may be unpleasant, even dangerous, undoubtedly costly and which will certainly cause parental anxiety.

Conclusion

As a necessary preliminary to diagnosing the abnormal, it is essential to be thoroughly conversant with the normal, with normal variations, and especially the reasons for those variations. The result of not knowing the normal brings much suffering for the child, unnecessary investigation, unnecessary medical treatment and surgical procedures, with inevitable anxiety for the parents. Douglas Gairdner's famous paper drew the attention of the world to one aspect of the normal which is still not known to many.

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'The decline and fall of hospital paediatrics' 23 years after

When Douglas Gairdner predicted the imminent decline and fall of hospital paediatrics he was assuming that in a relatively affluent and competent society, for which the zymotic diseases were losing their terrors, the inpatient units that we had developed would lose their *raison d'être* once the purposes for which they had been founded had been more or less achieved.[1]

Hospitals were originally places to which the indigent poor resorted when their homes could not provide the conditions needful for their care and cure, or where they were sent either because it was thought that they were infectious and therefore dangerous to the rest of the community or because the sufferer had become a charge on the parish. It was therefore only relatively late in the development of medical services that hospitals for children were founded since it could be assumed in most cases that their best care-takers would be their own families—unless they were foundlings or orphans—and that away from their families they were likely to pine rather than to recover.

The children's hospitals grew out of the dispensaries[2] that provided rudimentary primary care for those children whose poor parents were unable to pay for the services of a physician or apothecary when it was recognised that in many cases home conditions were such as to be inimical to their recovery or rehabilitation. But as in adult medicine, hospitals provided a setting in which physicians were able first to categorise and then to study scientifically the diseases that had led to admission; and this proved to be the essential preliminary to developing measures for prevention or treatment. Usually such physicians were generalists who, while earning their living in private practice, devoted their public practice to the study of a specialty—of which paediatrics became one. Thus initially paediatrics became the study of diseases peculiar to children rather than the general medicine of childhood; and this distinction is one that has ever since bedevilled the relations between paediatrics and what has now become adult medicine.

The separate development of the children's hospitals—such as the Royal Manchester Children's Hospital and Great Ormond Street, the children's wards in the general and university hospitals, the isolation hospitals whose clientele were mainly children, and the workhouses with their infirmaries, also led to divisions in paediatric practice which we are still trying to sort out and overcome. Generally, the children's hospitals succeeded in the task of identifying and arriving at some understanding of the illnesses of childhood as they then were, and in developing a corps of children's doctors, nurses, and ancillary workers with experience in dealing with children.

Paediatrics as a separate specialty developed late; it was difficult in Britain to earn a living from private paediatric practice, and it was only after the second world war, with the establishment of the NHS and the provision of free medical care for women and children, as well as for insured workmen, that physicians with an interest in the diseases of childhood and no private income were able to devote themselves totally to paediatrics: in fact Gairdner's generation must have been the first in which physicians could make it a full-time career. These physicians inherited the facilities and traditions of the various children's hospitals and units which had been developed throughout the country and, reinforced by refugees from countries with a tradition of paediatric practice (for instance in Manchester the institutions founded by Merei and Borchardt in the 1850s), and by experience in the great American paediatric hospitals, they were able to take full advantage of the therapeutic explosion that began with the development of effective chemotherapy. Thus within a decade their wards began to empty and paediatrics became, like chest medicine, one of the specialties which could be said to have fulfilled its mission.

This was the situation when Gairdner wrote his article; and its influence was the greater because of doubts about what may be called the negative aspects of hospital care; separation from home and family, the interruption of schooling, the need for constricting discipline in a busy ward, and the possibilities for cross-infection. It was the time when Bowlby's views on separation became common knowledge, when the St Mary's home care scheme was established, and when all-day visiting, hospital schools, and ultimately, facilities for play in hospital became *de rigueur*—changes which had the important side effect of totally altering the role of children's nurses from substitute mothers into the givers of support to visiting mothers (and injections) and which may be partly responsible for our present difficulties in recruiting children's nurses.

Donald Winnicott put it very well in an unpublished letter to Robert Tod defending the new attitudes: 'I became a Physician in charge of my own Department at the Paddington Green Children's Hospital in 1923 and retired after 40 years. In the course of that time there was a gradual shift in the work of the Department from physical illness to emotional disturbance or to the psychological aspect of the personality if one uses the word psychological without specifically linking it with academic psychology.

'At the same time I had an appointment of a similar nature in the decade 1923–33 in the East End at the Queen's Hospital for Children, now Queen Elizabeth's. Here I saw a very large number of patients and was in charge of the LCC Rheumatism Clinic which dealt with rheumatic fever and chorea and concomitant heart disease.

'We also had to deal with very severe summer diarrhoea and various polio epidemics and, of course, those were the days before antibiotics so that our wards were full of children with pus in the lungs, the bones, or the meninges. Penicillin put a stop to all that and transformed physical paediatrics into something which could afford to look at the disturbances that belong to the lives of children who are physically healthy. In a way, therefore, the advances of physical paediatrics opened up the field for child psychiatry. I tried to make full use of this new development.'

Many paediatricians still in practice will be able in their mind's eye to contrast the spick and span wards of their professional childhood with their rows of tidy beds and lockers, their institutionalised inmates, and their well-organised routines with the present informality. The substitution of an endo- for an exo-skeleton does not of course necessarily imply a loss of efficiency.

But structures are not so rigid that they cannot be adapted to new circumstances, and progress in medicine is like that of the hill walker who on gaining one summit gets his first view of the next. In more or less conquering the zymotic diseases and their after effects we gave ourselves the opportunity of tackling properly a whole range of problems including those of the handicapped child, those posed by the newborn baby, and those resulting from congenital abnormalities both structural and biochemical; moreover there is still plenty of work for a short-stay hospital ward whether in terms of investigation (such as those necessary to determine the aetiology of short stature), for observation (as in cases of unwell babies at risk of sudden death), for evaluation (as in cases of suspected inflicted injury), and for treatment (as in the case of status asthmaticus, diabetic keto-acidosis, leukaemia, and intensive care). Thus 45% of the sample of children followed in the National Child Development Study were admitted to hospital by age 7 years.[3]

The number of available beds has not in fact changed greatly though recently there have hardly been enough trained nurses to man them as a result of what we must consider mistaken policies emanating from the General Nursing Council. Administrators who measure efficiency by bed occupancy and who do not understand that bed occupancy and turnover are necessarily inversely related should be made to recognise that beds in which there is no turnover will always be occupied and that to ensure a good turnover with the minimal length of stay that is best for children and no waiting, a large proportion of beds must be free at any one time. In fact maximum usage of beds depends on filling them from a waiting list with minimum delay which is incompatible with coping efficiently with a large emergency load and is a great strain on nursing staff. The available beds could however be better used if no children were nursed in nonpaediatric wards (including those in isolation hospitals), which despite Platt they still are, and if we had enough trained nurses.

Thus it did not need the application of Parkinson's Law to keep the children's wards turning over.[4] We should be less complacent about the growing need to admit children with relatively trivial illnesses from materially 'good' homes because their mothers are at work and cannot look after them; but while women continue to believe that they will get the best rather than the worst of both worlds by trying to hold down a job as well as rearing a young family, the hospital will have to back up the nursery in this way. So it is that, contrary to Gairdner's prediction, the children's units remain nearly as busy as they ever were; and we are now less worried about separation which is mitigated by short-stays and all-day visiting and where ill effects have been shown to be related as much to home as to hospital conditions: indeed some children only thrive *in* hospital.[5]

What of the future? Looking at the present work of the paediatrician, it is clear that it comprises three main activities: the out- and inpatient care of acute and chronic illness, which includes investigation as well as nursing and treatment; involvement in child care in the home and at school, and especially with the assessment and amelioration of handicap; and the sometimes intensive care of the vulnerable newborn. We also need to recognise that our patients come from the maternity hospitals and are passed on to the general hospitals and that in the case of adolescents now surviving protracted and serious illness in childhood—such as cystic fibrosis, malignant disease, inborn error, muscular dystrophy etc.—the handover may be traumatic and can expose them to danger when neither the adult physician nor the GP is experienced in the kind of care that they need.

Paediatrics has now developed to the point where most physicians dealing with adult patients acknowledge that the paediatric physician has more to offer the sick child; and in these circumstances demarcation disputes should be a thing of the past with the paediatrician dealing with those children brought to the doctor by their parents or guardian and the internists with those seeking a consultation of their own volition. Some physicians may reasonably want to share the care of certain patients with their paediatric colleagues in the children's wards; and in exchange they should perhaps offer beds and help to paediatricians whose patients have outgrown the facilities of a children's unit! It seems obvious that isolated comprehensive children's hospitals will have less to offer in the future than units sharing a campus with obstetric and general hospitals; and that it should be acknowledged that adult medicine and paediatric medicine need also to share their knowledge (each has so much to learn from the other) in caring adequately for children with advanced organ system disease. In this field one foresees the development of combined medical and surgical units run jointly by paediatricians with an interest in an organ system and organ system specialists with an interest in children. Such a children's unit would need its own building (though with link corridors to the obstetric and general hospitals sharing the site), its own ancillary staff, a children's trained nursing staff not at the beck and call of senior nursing officers on the adult side, its school, and its subdepartments of radiology and pathology. It would operate mainly as a polyclinic with only enough beds—including day beds, planned investigation beds, observation beds, and an intensive care unit—to serve its outpatient department, assessment unit, and casualty departments; and the last would in city centres provide a hospital-based primary care service run by the local GPs or department of general practice.[6] The children's unit should also house the departments of child psychiatry and paediatric surgery and, very important, anaesthetics, and be closely linked with the department of genetics. The paediatric division would provide a forum for all those in paediatric care whether at primary, secondary, or tertiary level. Such a unit might well in most cases serve an area rather than a district, especially in conurbations, as well as making its regional contribution.

Identity having been acknowledged, collaboration between equals is possible and desirable. But in certain respects we need to maintain autonomy; and we have links with obstetrics as well as with medicine, surgery, and psychiatry. As a major part of general medicine (that of childhood) we have properly remained within the College of Physicians; but if, in order to regulate our training and to give representative advice to government, we need to establish our own faculty, we could perhaps ask the adult physicians in equity to do the same. As regards the British Paediatric Association, perhaps it could revert to its original aims—modelled on those of the Association of Physicians—of sharing advances in knowledge and promoting friendship between members. But if paediatrics is to continue to thrive, we must put the service and the discipline first in our loyalties and not our institutions however venerable and famous. Douglas Gairdner was right in seeing that an era had come to an end; but it was not that of hospital paediatrics but that of isolated paediatric hospitals. The future lies in collaboration with our colleagues in other specialties as well as with the development of our own specialties, for paediatricians are essentially general physicians both by inclination and because of the nature of most of their work, which is concerned with the origins rather than the results of disease. This is where our contribution to the prevention of ill health in adult life will be important; and perhaps in that context we can look forward to the decline and fall of all hospital medicine and even of the maternity hospitals.

In common with all paediatricians, I am indebted to Douglas Gairdner for making me think about the current problems and their possible solutions. I am grateful to Dr D. H. Vaughan of the Manchester Regional Health Authority for supplying the relevant national and regional statistics, and to Mr T. Ibison, Sector Administrator, Royal Manchester Children's Hospital, for allowing me to study Mr I. T. Wood's unpublished MSc thesis 'Report on RMCH. An OR-based examination of the performance characteristics of the Royal Manchester Children's Hospital'.

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Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children

Anticonvulsant effect and side effects

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SUMMARY In a prospective study 44 children, aged 6 months to 5 years, admitted to hospital with febrile convulsions or epilepsy, were treated with diazepam in solution administered rectally during 59 generalised attacks. Rectal administration of diazepam was effective in the acute treatment of convulsions in 80% of cases. In 10% the treatment failed, whereas diazepam administered intravenously had prompt effect; another 10% of the convulsions were resistant to diazepam, irrespective of the route of administration. The therapeutic effect was significantly correlated with the duration of convulsions before treatment started. Early treatment (convulsions $\leqq 15$ minutes) had effect in 96%, and late treatment (convulsions >15 minutes) in 57% of cases. A total of 317 children admitted with febrile convulsions were treated prophylactically with diazepam administered rectally whenever the temperature was $\geqq 38\cdot5$°C. No case of significant respiratory depression or other serious side effects was observed. The rapid and reliable anticonvulsant effect of diazepam given rectally and the very few side effects makes this treatment a valuable alternative to IV administration in childhood.

Diazepam given intravenously is one of the best anticonvulsants available for acute use. However, during convulsions in young children IV injections are often difficult or impracticable. An alternative route, therefore, is needed. Suppositories are of limited value in emergency treatment, the therapeutic plasma concentration not being reached until after about 20 minutes (Knudsen, 1977). The anticonvulsant effect of diazepam administered IM can be unreliable because of unpredictable absorption (Dundee *et al.*, 1974).

A solution of diazepam given rectally will be absorbed rapidly and almost completely (Agurell *et al.*, 1975) and anticonvulsant plasma concentrations are obtained within less than 4 ± 1 minutes (Knudsen, 1977). However, no clinical studies are available on the value of this route of administration in the acute treatment of convulsions and on the side effects (Dulac *et al.*, 1978).

Patients and methods

The prospective study took place between 1 October 1976 and 1 October 1978, during which period 349 children with febrile convulsions and 12 with epilepsy (Table 1), aged from 6 months to 5 years, received therapeutic or prophylactic diazepam, administered rectally, while in hospital. The acute anticonvulsant effect was assessed on the basis of the therapy group and the side effects on the basis of the prophylaxis group.

Acute treatment. A total of 44 children who had convulsions on arrival in the emergency ward or who developed convulsions during admission received acute treatment with diazepam given rectally during 59 generalised attacks. The duration of the convulsion after administration of the drug was registered by means of a stop watch. If the attack had not

Table 1 *Patients*

Diazepam	*No. of patients*		*No. of doses*
	Febrile convulsions	*Epilepsy*	
Prophylactic	317	0	583
Therapeutic	32 (35)*	12 (24)*	63
Total	349	12	646

*Number of attacks.

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ceased within 5 minutes rectal treatment was repeated or the child was given diazepam intravenously. Thus, the IV route was used only when rectal administration was unsuccessful.

Prophylactic treatment. A total of 317 children admitted with febrile convulsions received prophylactic treatment with rectal diazepam when the rectal temperature was $\geqq 38\cdot5$°C. All of them were monitored clinically with a view to development of respiratory depression or other serious side effects. In 225 of the children the respiratory rate was recorded before each administration of diazepam and 10 minutes later—that is, at the time when the plasma concentration is at its highest (Knudsen, 1977).

Diazepam administration and dosage. We used a prepackage containing a 2·5 ml disposable plastic syringe, a 6 cm long plastic tube with a blunt tip, and diazepam solution (Apozepam,* 5 mg/ml diazepam, ampoules of 2 ml). The solution used was the undiluted ordinary IV preparation. Similar doses were given therapeutically and prophylactically. Children aged $\leqq 3$ years received 5–7·5 mg diazepam rectally (0·5–0·9 mg/kg per dose), children >3 years were given 7·5–10 mg diazepam rectally (0·6–0·8 mg/kg per dose). The prophylactic treatment was repeated every 8–12 hours whenever the child had a rectal temperature of 38·5°C or above (1·0–2·7 mg/kg per 24 hours). In the prophylaxis group, 57% of the children received one dose, 34% between 2 and 3, and 9% of children between 4 and 6 doses over a period of 2–3 days.

Statistical methods. The P-values were calculated using the χ^2 test or Fisher's exact test.

Results

The anticonvulsant effect of diazepam given rectally is shown in Tables 2 and 3. A total of 44 children received this treatment during 59 attacks. In 5 of these cases no effect could be expected from rectal administration, the convulsions being resistant to diazepam—that is, they did not stop even after very high doses of diazepam intravenously (2–3 mg/kg per $\leqq 20$ minutes), which was given if rectal administration was unsuccessful. In 80–87% of the remaining cases (n=54) rectal administration had a satisfactory anticonvulsant effect, defined as cessation of convulsions $\leqq$ 5 minutes or $\leqq$ 10 minutes after administration (Table 2). This group included 7 (13%) patients with recurrences within 15 minutes of the first attack, the second fit stopping $\leqq 5$ minutes after administration of another dose. The therapeutic effect was significantly correlated with duration of the attack before treatment. Early treatment had effect in 96%, and late treatment in 57% of cases ($P<0\cdot001$) (Table 3).

Table 2 *Anticonvulsant effect of rectal administration of diazepam*

	Attacks		*Febrile convulsions*		*Epilepsy*	
	No.	*(%)*	*No.*	*(%)*	*No.*	*(%)*
Total no. of attacks	59		35		24	
Convulsions stopped after rectal administration						
$\leqq$5 minutes	43/54*	(80)	22/31	(71)	21/23	(91)
$\leqq$10 minutes	47/54	(87)†	26/31	(84)	21/23	(91)
No effect of rectal administration. Prompt effect of IV administration	7/54	(13)	5/31	(16)	2/23	(8)
No effect of rectal administration. No effect of IV administration‡	5/59	(9)	4/35	(11)	1/24	(4)

*5 out of 59 cases were resistant to diazepam, see text and‡.
†7 children had recurrences, see text.
‡Convulsions $\geqq$20 minutes after diazepam 2–3 mg/kg per $\leqq$20 minutes, administered intravenously.

Table 3 *Anticonvulsant effect of rectal administration of diazepam as a function of the duration of the convulsions before treatment*

Duration of convulsions before treatment	*No. of attacks*		*Convulsions stopped $\leqq$5 min after diazepam*		*P value*
	Febrile convulsions	*Epilepsy*	*No.*	*(%)*	
$\leqq$15 minutes	7	17	23/24	(96)	$<0\cdot001$
$>$15 minutes	28	7	20/35	(57)	
Total	35	24	43/59	(73)	

No case of clinically significant respiratory depression or other serious side effects was observed in the 317 children receiving prophylactic diazepam treatment. The respiratory rate did not change significantly ($P>0\cdot3$) on the 225 children examined, even after repeated doses of diazepam ($P>0\cdot3$). Sedation was common. In 2 patients who developed purulent meningitis during treatment the diagnosis was easily established, the stiffness in neck and back not being concealed by diazepam. In a third patient the possibility cannot be excluded that establishment of the diagnosis was delayed a few hours.

Discussion

Rectal administration of diazepam was effective in the acute treatment of convulsions in 80% of cases. In 10% the treatment failed, whereas diazepam given intravenously had prompt effect. In another 10% the convulsions were resistant to diazepam, irrespective of the route of administration (Ferngren, 1974). Early treatment was effective in 96%, and late treatment in 57% of cases. Consequently, rapid intervention must be considered a prerequisite for achieving optimal anticonvulsant effect.

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* Specially prepared by Apothekernes laboratory, Oslo, Norway.

For ethical reasons the study did not have an untreated control group. However, the obvious correlation between treatment and cessation of convulsions indicates a significant therapeutic effect. The pronounced agreement between clinical effect and pharmacokinetic properties (Agurell *et al.*, 1975; Knudsen, 1977) leads to the same conclusion. Lack of effect of rectal administration may be due either to poor absorption in a few cases or to convulsions which respond only to very high plasma concentrations.

No serious side effects were observed, even after repeated administration which gives rise to considerable accumulation of diazepam (Greenblatt and Shader, 1974). It remains to be clarified whether diazepam, which has a pronounced relaxing effect on muscles, may conceal stiffness in neck and back.

The rapid and reliable anticonvulsant effect and the very few side effects make the rectal route of administration a valuable supplement or alternative to IV administration in infants and children. In order of priority, according to therapeutic value, the various routes of administration of diazepam would be: IV injection, rectal administration in solution, IM injection, and suppositories.

In the prophylactic treatment of febrile convulsions (Knudsen and Vestermark, 1978) diazepam in solution offers hardly any advantages over suppositories. However, with the former, using the same medication, combined prophylactic and therapeutic control of convulsions is offered. Our experience shows that most parents with children suffering from febrile convulsions are able to treat their children at home prophylactically or in cases of recurrences. All hypnotics and psychosedatives, including benzodiazepines, have a potential respiratory-depressive effect. The treatment, which gives high plasma concentrations (Knudsen, 1977), should therefore only be given at home if the parents are carefully instructed (verbally, in writing, and by means of demonstrations), and if the child's reaction to the treatment has been studied during admission to hospital, in particular if the child is treated concurrently with phenobarbitone.

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Water loss from the skin of term and preterm babies

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SUMMARY Water loss from the skin of term and preterm babies, nursed naked in incubators under neutral thermal conditions, was measured by a method based on estimating the water vapour pressure gradient close to the skin surface. 199 sets of measurements were made on 78 babies whose gestational ages ranged from 26 to 41 weeks, during the first 4 weeks of life. Babies of 34 to 41 weeks' gestation had high water losses in the first 4 hours after birth, which then fell to low levels averaging 6 g/m^2 per hour. Babies of 30 to 33 weeks' gestation had high water losses in the first week which then fell to levels similar to those of mature babies. Babies <30 weeks' gestation had strikingly high losses, averaging 32 g/m^2 per hour in the first 4 days of life. At 2 weeks, levels were still higher than those of mature babies. Light-for-dates babies had skin water losses appropriate for their gestations. The high water losses in extremely preterm babies are probably transepidermal and the result of a thin, poorly keratinised stratum corneum. Water loss from the palms and soles was high in term babies and although low in preterm babies it rose steadily in the first 4 weeks of life. This is thought to represent the onset of emotional sweating. In terms of actual heat and water lost, skin water loss is relatively unimportant in term babies nursed naked under neutral thermal conditions. However, in babies <30 weeks' gestation, weighing <1 kg, skin water loss makes a major contribution to overall water balance. Furthermore, evaporative heat loss from the skin may exceed resting heat production. It is suggested that reduction of skin water loss in these babies may increase their chances of survival and their rates of growth.

Water loss from the skin of a newborn baby, either directly through the epidermis or from the sweat glands, may be important, firstly, as a source of heat loss and, secondly, as a major factor in overall water balance. Measurement of skin water loss from babies has been hampered in the past by the lack of a suitable method. Total insensible water loss from the skin and respiratory tract has been measured using a metabolic chamber (Hey and Katz, 1969; Zweymuller and Preining, 1970), or by measurement of weight loss (Levine *et al.*, 1930; Fanaroff *et al.*, 1972; Wu and Hodgman, 1974; Marks *et al.*, 1977). Measurements of skin water loss from isolated sites have been made using a ventilated capsule (Foster *et al.*, 1969; Cunico *et al.*, 1977). Results suggest that skin water loss is low in term babies, but that in preterm ones, whether nursed naked in standard incubators or under radiant warmers or phototherapy, losses are high.

Nilsson (1977) described a method for measuring water loss from the skin, based on estimation of water vapour pressure gradient close to the skin surface. Hammarlund *et al.* (1977) used this method to measure transepidermal water loss in term infants nursed naked in incubators under neutral thermal conditions and found that it decreased as the ambient humidity was increased. They also measured rates of evaporation from several sites in a small number of babies on the first day of life and found that while rates were high on the face and extremities, they were generally low elsewhere. We were interested in using this simple method to examine the rates of skin water loss from different parts of the body in both term and preterm infants, and to see how they changed with postnatal age.

Method

Evaporation rate (ER) of water from the skin was measured using the commerically available apparatus devised by Nilsson, the Evaporimeter EP1 (Servomed). This measures the water vapour

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pressure gradient close to the skin surface which is directly proportional to ER. The method has been described in detail (Nilsson, 1977). The relative humidity sensors were calibrated by placing the probe in atmospheres of known humidity.

Measurements were made on naked babies in a standard single-walled incubator with a proportionally controlled heater (59 or 79, Vickers Medical) the air temperature of which was set close to the lower end of the thermoneutral range, according to the values reported by Hey (1971). Several very low birthweight babies in the first week of life required incubator air temperatures in excess of 36·9°C to maintain normal rectal temperatures, these temperatures being the maximum obtainable when using the incubator in the air mode. In these cases, servo-control was used, setting the abdominal skin temperatures to 36·5–36·9°C and allowing the air temperature to rise to 39°C if necessary. Measurements were made on the quiet or sleeping baby through the portholes of the incubator at least 20 minutes after any adjustment to incubator temperature. The ER from a small area of skin (approximately 1 cm^2) was measured by lightly resting the probe on the baby's skin until a stable reading was obtained. To avoid errors due to moisture on the investigator's hands, rubber gloves were worn. ER in g/m^2 per hour was measured at 18 different skin sites in all babies: forehead and cheek representing the head (21%), chest and abdomen (14%), back (13%), buttock (5%), anterior and posterior surfaces of the upper arm (8%), and lower arm (6%), palm and dorsum of the hand (5%), anterior and posterior surfaces of the thigh (11%), and lower leg (10%), and the sole and dorsum of the foot (7%). The figures in brackets represent the percentage of the total surface area contributed by the various sites in newborn babies (Lund and Browder, 1944).

The rectal temperature was measured in term babies with a mercury thermometer inserted approximately 4 cm into the rectum and in preterm babies with a thermocouple probe inserted approximately 8 cm into the baby's rectum. The relative humidity within the incubator was not controlled but was measured with the Evaporimeter probe and recorded. The incubator air temperature was measured with a thermocouple placed in the centre of the incubator. Skin temperature was measured by a thermocouple lightly taped to the upper abdomen. The gestational age of the baby was calculated in completed weeks of pregnancy from the first day of the mother's last menstrual period. In addition, in the preterm babies (37 weeks' gestation or less) a gestational assessment was carried out using a scoring system based on external characteristics (Farr *et al.*, 1966). Results were not included if there was a wide discrepancy between the assessed gestational age and that based on the mother's menstrual data. Babies were judged either appropriate or light-for-dates using the 10th centile on the charts of Babson *et al.* (1970) and Thomson *et al.* (1968).

Subjects

The babies were divided into four groups according to gestational age.

Group 1 (38–41 weeks). 57 sets of measurements were made on 36 healthy, term babies, all appropriate for dates, aged from 2 hours to 10 days. Mean birthweight was 3·31 kg (range 2·60–4·36).

Group 2 (34–37 weeks). 29 sets of measurements were made on 16 healthy babies, aged from 2 hours to 21 days. Nine babies were light-for-dates. Mean birthweight was 2·08 kg (range 1·07–2·90).

Group 3 (30–33 weeks). 65 sets of measurements were made on 16 healthy babies, aged from 2 hours to 27 days. Four babies were light-for-dates. Mean birthweight was 1·43 kg (range 1·01–2·20).

Group 4 (<30 weeks). 48 sets of measurements were made on 10 babies, aged from one hour to 25 days. All were appropriate for dates. Eight of the 10 babies were unwell with either recurrent apnoea or respiratory distress syndrome during at least one of the sets of measurements. They were receiving oxygen and intravenous fluids. Six babies were receiving intermittent positive pressure ventilation when studied. Six of the 10 babies died. Mean birthweight was 0·89 kg (range 0·66–1·34). Gestational ages ranged from 26 to 29 weeks.

Results

The babies were studied at ambient temperatures judged to be close to the lower end of the thermoneutral range (Table 1). Room air temperature varied between 25 and 30° C and thus the operative environmental temperatures, allowing for radiant heat exchanges, were probably about 1°C less than the actual incubator air temperatures (Hey and Mount, 1966). The mean abdominal skin and rectal temperatures of babies below 30 weeks' gestation in the first week of life were lower than those of more mature infants in spite of high incubator air temperatures and, in many instances, the baby's surface and rectal temperatures were below that of the surrounding air. Relative humidity varied between 27 and 63% and mean values in each group of babies were similar.

Table 1 *Mean incubator air, abdominal skin and rectal temperatures, and mean ambient relative humidity in the four groups of babies*

Group	*Postnatal age (days)*	*Incubator air temperature (°C)*			*Abdominal skin temperature (°C)*			*Rectal temperature (°C)*			*Relative humidity of incubator air %*		
		Mean	*SD*	*Range*	*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*
1 (38–41 weeks)	0–11	33·1	0·5	32·0–34·5	35·8	0·5	34·8–36·8	37·0	0·4	35·8–37·8	47	5	33–60
2 (34–37 weeks)	0–6	34·5	1·2	33·1–36·6	36·4	0·5	35·2–37·0	36·9	0·5	35·7–37·4	42	4	37–55
	7–21	33·5	0·7	32·5–34·5	36·8	0·5	36·0–37·5	37·3	0·4	36·7–37·7	41	6	29–48
3 (30–33 weeks)	0–6	35·7	1·0	32·7–37·1	36·8	0·4	35·9–37·9	37·1	0·4	36·3–38·3	44	7	30–59
	7–27	34·0	1·4	31·6–36·7	36·7	0·4	35·7–37·7	37·2	0·3	36·7–37·8	43	5	28–55
4 (<30 weeks)	0–6	37·4	1·5	34·0–40·1	36·3	1·0	33·3–37·6	36·7	0·9	33·7–38·4	42	5	33–56
	7–13	36·7	2·4	31·1–39·5	36·7	0·5	35·9–37·4	37·1	0·4	36–6–37·9	39	7	28–47
	14–25	34·8	2·5	31·2–38·5	36·7	0·7	36·0–37·7	37·1	0·5	35·9–37·9	46	12	27–63

Overall skin water loss. An overall water loss, representative of the loss from the baby's skin as a whole, was obtained by multiplying each of the 18 measurements of ER by the percentage contribution that the measurement site made to total surface area and then adding these together. Results were examined for each group of babies.

Group 1 (Fig. 1)

Water losses in this group were low. Measurements made in the first 4 hours averaged 10·5 g/m² per hour but after this values fell. Average skin water loss after the first 4 hours was 5·9 ± 1·3 g/m² per hour (mean ± SD).

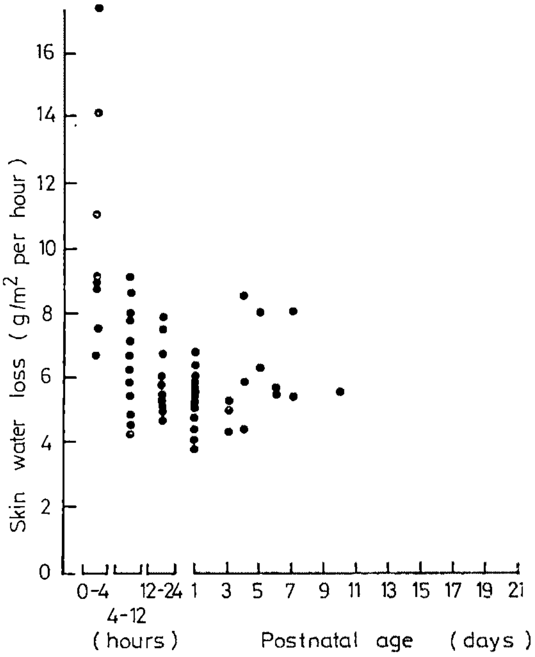

Fig. 1 *Skin water loss for babies of 38 to 41 weeks' gestation.*

Group 2 (Fig. 2)

Water losses in this group were also low and values were similar to those found in term babies. Measurements made in the first 4 hours averaged 11·0 g/m² per hour. After this time the average skin water loss was 6·0 ± 1·2 g/m² per hour. Babies who were light-for-dates did not differ from those who were appropriate for dates.

Group 3 (Fig. 3)

Skin water losses were considerably higher than in term babies and the fall in values after 4 hours of age was not seen. Average losses in the first week were 13·0 ± 3·5 g/m² per hour, but from the second week onwards were similar to those in term babies (7·8 ± 1·7 g/m² per hour). Babies who were light-for-dates did not differ from those who were appropriate for dates.

Group 4 (Fig. 4)

Skin water losses in these extremely preterm babies were very much higher than those seen in term ones, and again the fall in values after 4 hours of age was not seen. In the first 3 days losses averaged 32·4 ± 13·6 g/m² per hour. Losses were still high after the first week; 3 out of 5 babies studied serially at this time had losses 2 to 4 times greater than those of mature babies. Average losses from 4 to 7 days of age were 21·5 ± 8·0 g/m² per hour, from 8 to 14 days 15·7 ± 7·6 g/m² per hour, and from 15 days onwards 11·4 ± 4·8 g/m² per hour.

Water loss from individual sites (Table 2). As would be expected, the rates of evaporation at individual sites fell as both gestational age and postnatal age

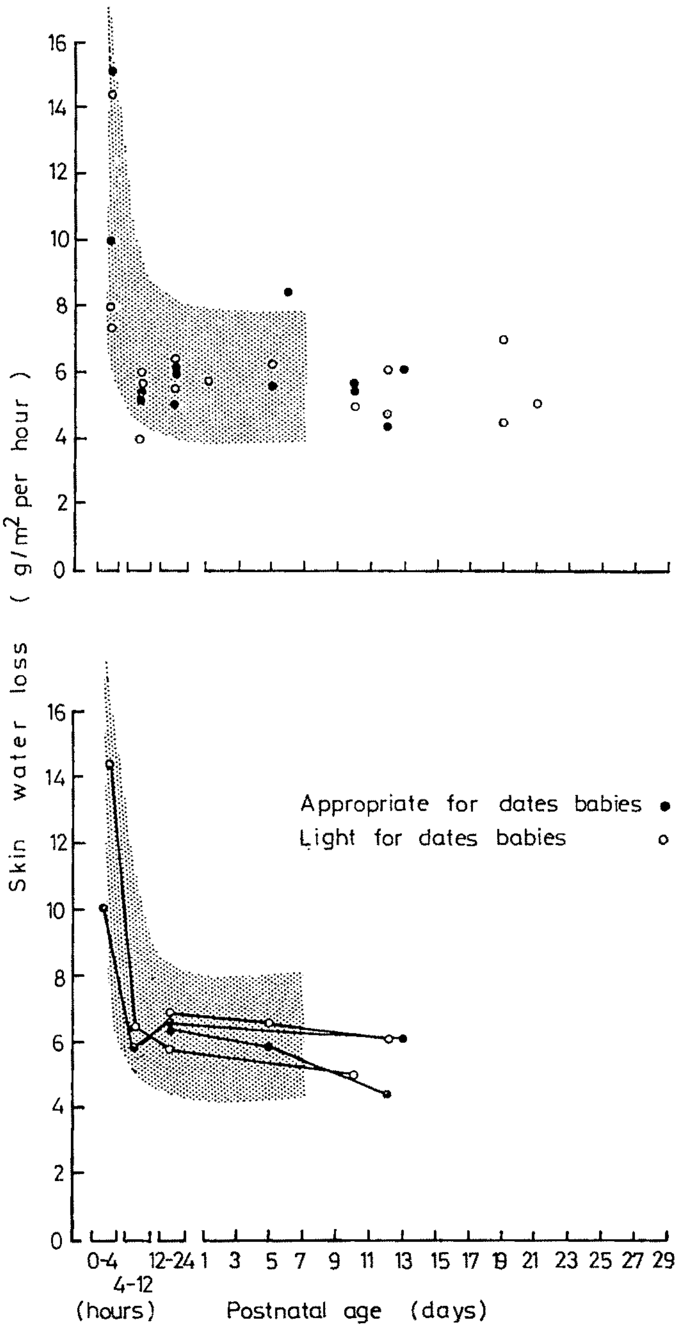

Fig. 2 *Skin water loss for babies of 34 to 37 weeks' gestation. Upper figure shows all the measurements made on babies in this group. Lower figure shows those measurements which were made serially on the same baby. Hatched area represents the range of skin water loss found in term babies (Fig. 1).*

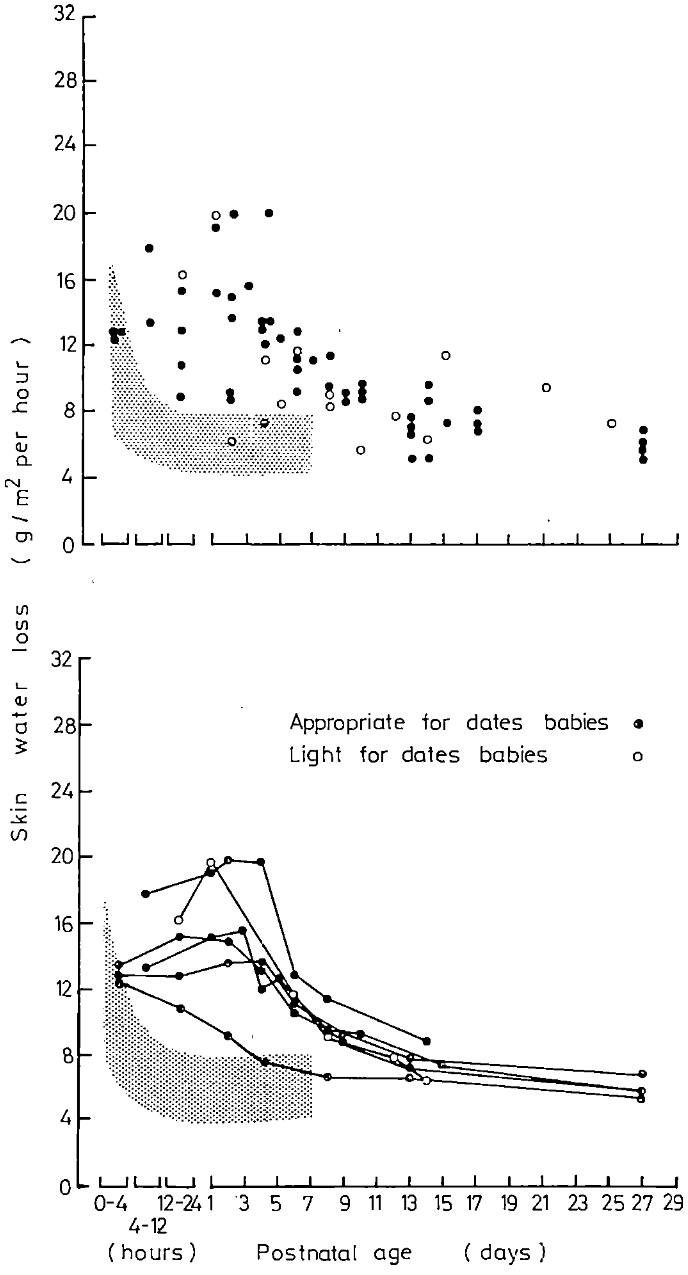

Fig. 3 *Skin water loss for babies of 30 to 33 weeks' gestation.*

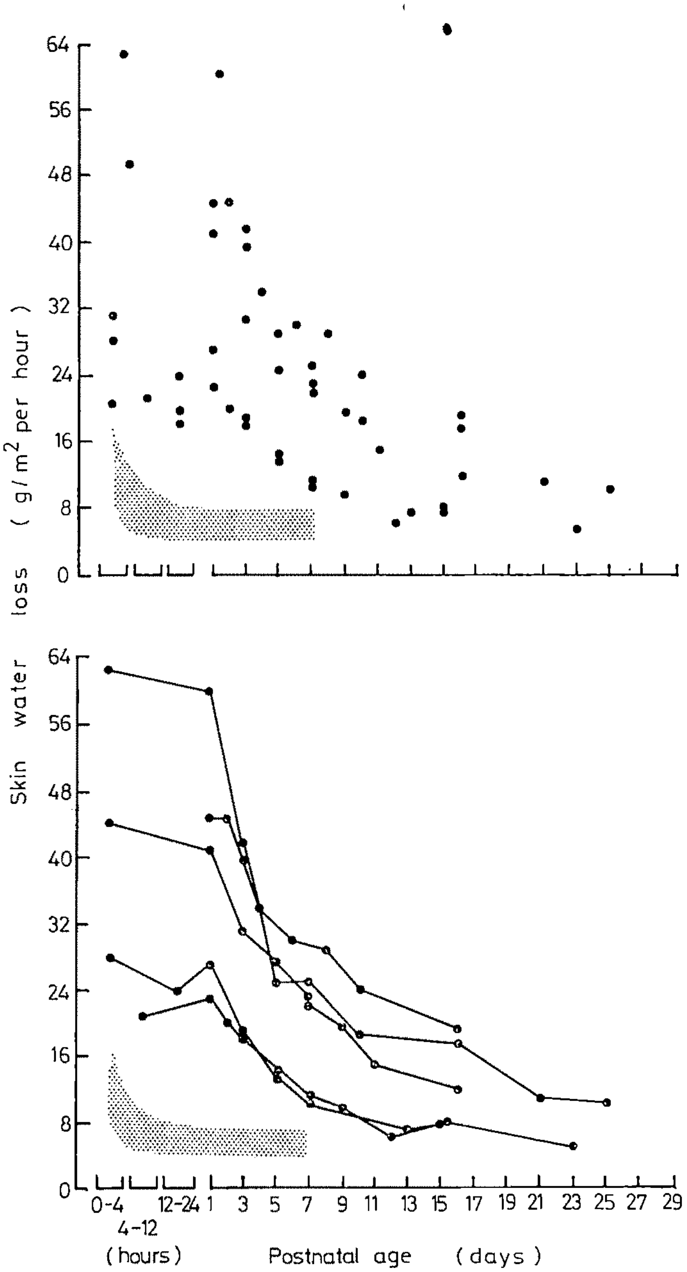

Fig. 4 *Skin water loss for babies <30 weeks' gestation.*

increased. A number of interesting findings emerged. In the most immature group of babies (group 4) the highest rate of water loss was found on the abdomen (Fig. 5). Lowest losses were found on the cheek, forehead, palm, and sole. As the babies grew older, all losses fell with the exception of those from the palm and the sole where water loss actually increased. A similar rise in water loss from these sites as the babies grew older was seen in the other preterm babies (groups 2 and 3). Term babies (group 1) had low rates of evaporation over most of the body but water losses from the palms and the soles were high.

Table 2 *Mean rates of evaporation at 18 different skin sites according to the gestational and postnatal age of the baby (g/m² per hour)*

Gestational age (weeks)	*0–6 days*			*7–13 days*			*14–20 days*			*21–27 days*		
	Mean	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*
Forehead												
<30	14·4	6·2	27	10·0	5·7	12	7·4	2·5	5	4·7	—	3
30–33	9·0	3·7	34	6·3	2·0	17	8·0	3·7	8	5·3	1·4	6
34–37	12·2	16·5	19	5·1	1·6	8	—	—	—	—	—	—
38–41	6·7	3·8	54	—	—	—	—	—	—	—	—	—
Cheek												
<30	19·3	8·9	27	12·3	6·8	13	10·8	—	4	4·3	—	3
30–33	9·7	3·3	34	6·4	1·5	17	6·8	2·4	9	5·5	1·1	6
34–37	5·7	2·3	19	5·9	3·1	8	—	—	—	—	—	—
38–41	5·9	1·8	54	—	—	—	—	—	—	—	—	—
Chest												
<30	25·9	12·8	26	17·0	7·0	14	14·6	7·1	5	8·7	—	3
30–33	11·2	3·5	32	7·5	2·3	17	7·2	2·1	9	6·3	0·5	6
34–37	6·1	2·0	19	5·1	1·4	8	—	—	—	—	—	—
38–41	6·0	2·3	54	—	—	—	—	—	—	—	—	—
Abdomen												
<30	51·1	30·5	27	23·0	12·7	14	16·4	4·7	5	10·0	—	3
30–33	15·2	5·8	34	8·9	2·3	16	9·9	3·2	8	7·8	1·9	6
34–37	7·7	1·8	19	5·9	1·9	8	—	—	—	—	—	—
38–41	5·7	1·9	54	—	—	—	—	—	—	—	—	—
Back												
<30	40·5	25·3	26	17·4	8·7	14	12·4	8·3	5	8·0	—	3
30–33	14·2	4·8	34	7·1	1·8	17	6·2	1·4	8	5·5	1·1	6
34–37	7·3	2·3	18	4·9	1·8	8	—	—	—	—	—	—
38–41	5·8	1·9	54	—	—	—	—	—	—	—	—	—
Upper arm-front												
<30	36·2	17·8	27	19·2	9·2	14	16·6	8·3	5	13·7	—	3
30–33	15·7	5·1	34	9·5	2·9	17	7·9	2·8	9	6·2	1·8	6
34–37	7·6	3·8	19	4·9	2·7	8	—	—	—	—	—	—
38–41	8·1	6·2	54	—	—	—	—	—	—	—	—	—
Lower arm-front												
<30	37·7	19·0	27	22·1	13·3	14	16·2	6·4	5	16·0	—	3
30–33	16·3	5·0	34	10·8	4·5	17	9·8	3·0	9	6·5	1·4	6
34–37	7·4	2·4	19	5·8	2·4	8	—	—	—	—	—	—
38–41	6·4	3·1	53	—	—	—	—	—	—	—	—	—
Lower leg-front												
<30	36·1	16·1	26	17·6	9·6	14	11·0	3·2	5	10·7	—	3
30–33	15·1	5·1	34	9·1	3·0	17	7·1	2·5	8	5·5	1·1	6
34–37	6·5	1·9	19	5·7	1·8	8	—	—	—	—	—	—
38–41	5·2	1·8	54	—	—	—	—	—	—	—	—	—
Lower leg-back												
<30	35·4	16·2	26	15·2	7·4	14	14·1	7·1	5	11·0	—	3
30–33	16·1	6·9	33	8·5	2·4	17	7·1	2·1	8	5·5	1·1	6
34–37	5·9	1·4	18	5·5	1·8	8	—	—	—	—	—	—
38–41	4·6	1·3	54	—	—	—	—	—	—	—	—	—
Palm												
<30	16·8	6·6	27	16·6	6·4	14	17·4	6·8	5	21·7	—	3
30–33	11·9	6·4	34	13·3	4·7	16	14·8	6·1	9	13·7	3·1	6
34–37	13·0	3·8	19	14·3	5·2	8	—	—	—	—	—	—
38–41	26·5	16·3	53	—	—	—	—	—	—	—	—	—
Upper arm-back												
<30	31·2	15·3	26	14·2	6·4	14	11·6	5·0	5	7·3	—	3
30–33	11·9	4·6	34	7·9	2·0	17	7·0	3·0	9	4·7	0·8	6
34–37	5·7	1·8	13	4·7	1·7	8	—	—	—	—	—	—
38–41	5·1	2·2	54	—	—	—	—	—	—	—	—	—
Lower arm-back												
<30	34·3	15·7	27	15·4	6·6	14	11·6	4·7	5	7·7	—	3
30–33	14·9	4·9	34	9·1	3·0	17	8·1	2·6	9	4·2	1·3	6
34–37	6·1	0·7	18	4·8	1·8	8	—	—	—	—	—	—
38–41	5·1	2·3	54	—	—	—	—	—	—	—	—	—
Dorsum of hand												
<30	29·4	10·1	26	19·0	7·1	14	12·6	5·1	5	10·3	—	3
30–33	15·2	4·8	34	10·4	3·9	17	10·2	3·1	9	6·8	1·9	6
34–37	6·1	1·9	18	5·3	2·1	8	—	—	—	—	—	—
38–41	5·2	2·4	53	—	—	—	—	—	—	—	—	—

Table 2—*continued*

Gestational age (weeks)	*0–6 days*			*7–13 days*			*14–20 days*			*21–27 days*		
	Mean	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*
Buttock												
<30	36·2	15·5	25	21·5	10·7	12	12·8	5·8	5	11·0	—	3
30–33	16·7	5·8	34	10·9	3·7	16	9·1	2·4	9	8·3	4·7	6
34–37	7·9	2·9	18	7·3	2·1	8	—	—	—	—	—	—
38–41	5·4	1·7	54	—	—	—	—	—	—	—	—	—
Thigh-front												
<30	32·9	13·8	26	22·2	12·1	14	14·6	7·0	5	10·0	—	3
30–33	14·8	5·1	34	9·8	2·8	17	7·9	1·9	9	7·5	1·8	6
34–37	7·3	3·2	19	6·0	2·0	8	—	—	—	—	—	—
38–41	6·9	3·8	54	—	—	—	—	—	—	—	—	—
Thigh-back												
<30	32·9	12·4	26	16·1	7·8	14	12·0	5·5	5	9·0	—	3
30–33	14·0	5·0	33	8·1	2·5	17	6·8	1·8	8	6·7	2·3	6
34–37	6·1	1·4	18	6·0	1·4	8	—	—	—	—	—	—
38–41	4·9	1·6	54	—	—	—	—	—	—	—	—	—
Sole												
<30	12·1	4·5	27	12·2	4·0	14	16·4	9·0	5	15·0	—	3
30–33	8·2	2·0	34	9·2	1·5	17	11·0	1·9	9	10·5	1·5	6
34–37	7·6	2·5	19	9·3	2·6	8	—	—	—	—	—	—
38–41	11·0	5·3	54	—	—	—	—	—	—	—	—	—
Dorsum of foot												
<30	28·3	13·8	27	17·4	8·2	14	11·0	4·7	5	7·3	—	3
30–33	12·4	4·3	34	9·1	3·0	17	7·4	2·7	9	6·0	1·3	6
34–37	5·6	1·8	19	5·6	1·1	8	—	—	—	—	—	—
38–41	4·6	2·1	54	—	—	—	—	—	—	—	—	—

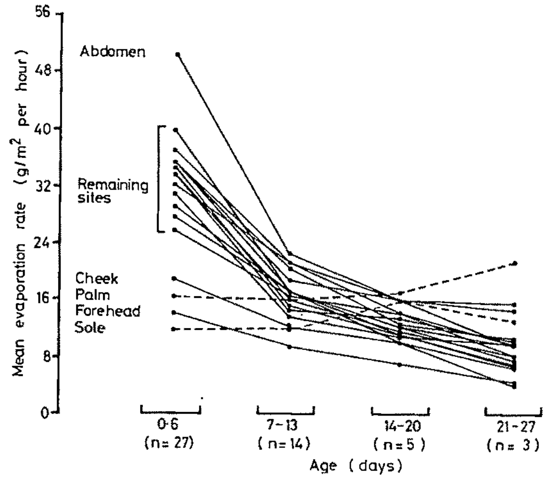

Fig. 5 *Mean rates of evaporation of water at 18 skin sites for babies <30 weeks' gestation.*

Discussion

It was perhaps surprising to find that the skin water loss of mature infants after the first 4 hours of life was lower than that of adults. Lamke *et al.* (1977) using Nilsson's method found average values in supposedly nonsweating adults to be about 12 g/m^2 per hour, compared with our values of 6 g/m^2 per hour in mature infants. In adults, over most areas water loss was about 8 g/m^2 per hour, but higher values of 20, 35, and 80 g/m^2 per hour were obtained from the forehead, soles, and palms respectively. Cunico *et al.* (1977) suggested that the higher values at these sites in a comfortable thermal environment were due to mild sweating. In both adults and babies, skin water loss and basal metabolic rate are directly related (Levine and Marples, 1930; Hey and Katz, 1969), so the higher water loss in adults might simply be due to the fact that they have higher metabolic rates per unit surface area than babies.

In both adults and term infants skin water loss was relatively higher from the palms of the hands and the soles of the feet (Hammarlund *et al.*, 1977; Lamke *et al.*, 1977) and we have confirmed this in term infants. Water loss from these sites is thought to be due mainly to sweating since the skin here is too thick to allow a high transepidermal water loss. This mental or emotional sweating is outside thermal control and is present over a wide range of ambient temperatures.

In the first 4 hours of life, the skin water loss in babies in groups 1 and 2 (34 to 41 weeks' gestation) was high and showed wide individual variation. All these babies were dried after birth with a warm towel and were not obviously wet when measured at least 2 hours later. The rates of water loss subsequently fell, suggesting that the surface of the skin was still drying out. It is well recognised that evaporative water loss plays a major part in the fall in body temperature which commonly occurs after birth.

Strikingly high losses were found in the immature babies. The more immature the baby, the higher was the skin water loss. Losses in babies who were light-for-dates were appropriate for their gestations. The highest skin water loss, about 60 g/m^2 per hour, was from a baby of 26 weeks' gestation weighing 660 g on the first 2 days of life. Several investigators have studied water loss in preterm infants, and various methods have been used. Hey and Katz (1969) measured the total evaporative water loss of naked term and preterm babies in a metabolic chamber and derived a skin loss from this by subtracting the measured respiratory loss. Although their study included a baby weighing 1·1 kg at 28 weeks' gestation, no difference in water loss between term and preterm infants was shown. However, Fanaroff *et al.* (1972), Wu and Hodgman (1974), and Marks *et al.* (1977) measured the insensible weight loss of preterm infants nursed naked in incubators using a sensitive balance and found relatively high weight losses, the average value of about 30 g/m^2 per hour in babies weighing <1·25 kg. Ambient temperature and humidity conditions were similar to ours. In magnitude these values are close to our own, which demonstrates that the higher weight losses of preterm babies are largely a consequence of water loss through the skin as opposed to the respiratory tract.

Although theoretically possible, it seems unlikely that the high losses in immature babies are a result of active sweating. Sweating in response to thermal stimuli has not been demonstrated in infants <210 days' postconceptual age (Foster *et al.*, 1969). Furthermore, in our study the most immature babies in the first week of life who showed the highest water losses, had lower skin and rectal temperatures than term babies (Table 1). Term babies had low water losses and were clearly not sweating. Water loss from the skin in immature babies is therefore predominantly transepidermal. Transepidermal water loss depends on two factors: the permeability of the epidermis to water, and the environmental conditions. The ambient temperature and water vapour pressure were similar in the term and preterm babies and cannot account for the high losses. The skin and rectal temperatures were often lower in the most immature babies which would tend to reduce transepidermal water loss. The high water losses can therefore only be explained by the properties of the epidermis itself. It has been demonstrated that the water-retaining properties of the epidermis are fairly evenly distributed throughout the stratum corneum. The dried, compact cells of the stratum corneum have a much greater resistance to water diffusion than the deeper aqueous epidermal cells (Scheuplein, 1972). The fibrous protein, keratin, which is the major constituent of the stratum corneum is thought to be the main barrier to water diffusion. The skin of the preterm baby looks and feels thin, these features being used in the assessment of gestational age. In the very immature baby <30 weeks' gestation it appears moist and the dermal blood vessels are easily visible. The stratum corneum is poorly developed and keratinisation, even of the palms and soles, does not occur until the 6th or 7th month of fetal life (Ernst, 1896). It seems likely therefore that the high water loss of preterm babies is the result of a lack of keratin. A preterm infant is a water-dwelling fetus forced to live in air; his skin must make premature adjustments to the new air interface. The more immature the infant, the greater the leak of water, and the longer it takes after birth for the leak to stop. However, even in the most immature babies, skin water loss falls to levels similar to those found in term babies after 2 or 3 weeks. This suggests that postnatal existence hastens functional maturation of the skin, possibly by stimulating the formation of keratin. It is consistent with the observation that the skin of extremely immature babies looks similar to that of a term infant by the time the baby is about one-month old

It is interesting that the highest rate of water loss in the most immature babies was found over the abdomen where the skin looks thinner and more transparent than at any other site. Similarly, the skin of the forehead, cheek, palms, and soles, which looks thicker than elsewhere, showed a lower permeability to water. Water loss from the palms and soles increased as the babies grew older, whereas losses at all other sites decreased. Furthermore, losses from palms and soles were higher in term babies. It seems likely that a proportion of the water evaporating from the skin of the palm and the sole in preterm babies in the first month is derived from sweat glands and represents the onset of emotional sweating.

Implications

From a knowledge of the surface area and the resting oxygen consumption of a baby, it is possible to estimate the total water loss from a baby's skin and the proportion of the baby's resting heat production that this evaporative heat loss represents (Table 3). Thus a term, 3·5 kg baby, one-day old, nursed naked in an incubator loses about 30 ml water from the skin each day (8 ml/kg per day). In terms of heat loss, this is equivalent to about 10% of the resting heat production. Clearly, water loss from the skin of a term baby is not of major

Table 3. *Estimated effects of skin water loss in two babies, one term (Case 1) and one extremely immature (Case 2), aged one day. Water and evaporative heat loss are low in Case 1. Case 2 however, has a high daily water loss and his evaporative heat loss from the skin exceeds his resting heat production. Even if his heat loss by radiation and convection is abolished, he must increase his heat production in order to maintain his body temperature*

	Case 1 (*3·5 kg, 40 weeks' gestation*)	*Case 2* (*0·9 kg, 28 weeks' gestation*)
Surface area (m^2) (Boyd, 1935)	0·2	0·1
Resting oxygen consumption (ml O_2/kg per min) (Hey, 1969)	6·5	5·5
Skin water loss (g/m^2 per hour)	6	32
Evaporative heat loss* from the skin (watts)	0·8	2·2
Resting heat production† (watts)	7·7	1·7
Evaporative heat loss from the skin as a % of heat production	$\frac{0\cdot 8}{7\cdot 7} \times 100 \simeq 10\%$	$\frac{2\cdot 2}{1\cdot 7} \times 100 \simeq 130\%$

*Latent heat of evaporation of water 580 cal/ml.
†1 ml O_2 = 4·83 cal.

importance once the skin has been dried after delivery. This however is not so for the very low birthweight, immature baby with a relatively high surface area in relation to body weight. A baby <30 weeks' gestation, weighing 0·9 kg, one-day old, nursed naked in an incubator loses about 75 ml water from the skin each day (about 85 ml/kg per day). In terms of evaporative heat loss, this exceeds his resting heat production. Hence, even if radiant and convective heat losses are eliminated, the baby can only maintain his body temperature by increasing his heat production. If the capacity to do this is limited, his body temperature will fall. This explains a clinical paradox. A very small immature baby nursed naked in an incubator frequently has a low rectal temperature. If radiant heat losses are eliminated by use of a Perspex radiant heat shield (Hey and Mount, 1966) and convective heat losses are abolished by raising the incubator air temperature to that of the baby's skin, the baby may still remain cold. This is because his high evaporative heat loss is greater than his maximum rate of heat production.

Controlled trials have shown that keeping small, 1–2 kg babies warm increases their chances of survival (Silverman *et al.*, 1958; Day *et al.*, 1964) and results in an increased rate of growth (Glass *et al.*, 1969). Immature babies, <1·0 kg birthweights have a very high mortality rate, while their rate of growth in the first few weeks of life is often extremely poor. If the high evaporative water losses from the skin of these immature babies were greatly reduced, their chances of survival and their growth rates might be considerably improved.

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Role of viruses in febrile convulsions

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SUMMARY A disseminated viral illness was demonstrated by isolating a virus from the CSF, blood, or urine in 27% of 73 children who were admitted to hospital after a first febrile convulsion However, a viral aetiology could be implicated for 86% of the children after combining results of tissue culture, electron microscopy, mouse inoculation, complement fixation tests, and interferon assay. Parallel bacterial cultures showed a possible pathogen in 29% of children, but in only 4% was the pathogen isolated from the CSF, blood, or urine. No correlation was found between the nature of the pathogen (or evidence of its dissemination) and the severity of the convulsion, degree of fever, CSF protein, CSF white cells, or the WBC. The results suggest that a febrile convulsion could be a response to invasion of the blood stream or central nervous system by a micro-organism which is usually a virus. Invasion may be of such brief duration that successful isolation of the virus from the blood, CSF, or urine is not more commonly achieved.

Between ages 6 months and 5 years about 3% of all children suffer at least one convulsion in association with a febrile illness (Lennox-Buchtal, 1973; Nelson and Ellenberg, 1978). There is now greater understanding of the chemical and structural characteristics of the immature brain and of the role of pyrogens in the pathogenesis of fever, but no direct link has been discovered between the febrile and the convulsive state (Lennox, 1953; Ounsted, 1976a). It has been suggested that the convulsion depends on the nature of the infecting micro-organism in combination with fever, age, and genetic predisposition. Epidemiological studies from western Europe and the USA suggest that febrile convulsions are associated with upper respiratory tract infections and other illnesses which are assumed to be due to viruses (Miller *et al.*, 1960; Millichap, 1968; Lennox-Buchtal, 1973). Even if there is no convulsion, viral illnesses can produce abnormal neurological signs, and slowing of the EEG pattern, without detectable changes in the CSF (Wallace and Zealley, 1970). The febrile convulsion might be a cerebral manifestation of a generalised viral illness or even a direct effect of virus on the central nervous system.

In a study from Nigeria about half the cases of febrile convulsions were associated with malaria parasitaemia, but enteroviruses were isolated from the blood or CSF in 8 out of 105 children on whom virus isolation tests were performed (Familusi and Sinnette, 1971; Familusi *et al.*, 1972). Most other reports of the viruses identified in association with febrile convulsions have been limited to isolates from the throat or faeces or to serological tests (Wallace and Zealley, 1970; Stokes *et al.*, 1977). The aim of this study was to establish a viral diagnosis and to find viruses in the CSF, blood, or urine immediately after the convulsion.

Patients and methods

The study lasted from 1 November 1976 to 1 December 1977. The patients were between ages 6 months and 5 years and were admitted with a generalised or focal convulsion associated with a rectal temperature of at least 38°C recorded in hospital within 24 hours of the convulsion. None of the children had had a previous convulsion.

Every child was seen within 24 hours by the same clinician, who recorded, on a standard proforma, the medical and developmental history, the findings on examination, and a clinical diagnosis of the illness which accompanied the convulsion. Each patient was reviewed daily in hospital and again in outpatients department 3 weeks later.

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Virological methods. Viral infections were detected by inoculation of tissue cultures, intracerebral inoculation of suckling mice for Coxsackie A viruses, electron microscopy for rotavirus, complement fixation tests, and interferon assay.

For viral cultures each prepared specimen was inoculated on to human embryonic lung fibroblasts (MRC5), Ohio HeLa cells, and secondary monkey kidney cells (Lewis *et al.*, 1979). CSF and heparinised blood were immediately inoculated into the tissue cultures and incubated in the treatment room where lumbar puncture and venepuncture were performed. Throat swabs in viral transport medium were kept at 4°C, and within 2 hours most were inoculated into tissue culture. Nasopharyngeal secretions were collected, as well as throat swabs, from 28 patients who entered the study after May 1977. Urine and stool specimens which could not be inoculated within 2 hours were stored at −70°C until inoculation. Faeces were suspended in nutrient broth, clarified by centrifugation, and the final supernatant was used for tissue culture, electron microscopy (Lewis *et al.*, 1979), and mouse inoculation.

Faecal specimens were screened for Coxsackie A viruses by intracerebral inoculation of litters of suckling mice on their first day of life (Melnick *et al.*, 1969). Throat swabs or nasopharyngeal secretions were used to screen those patients from whom no stools were obtained. When a screening specimen was positive all available specimens from other sites of that patient were examined.

Serological tests were performed on serum which was collected on admission, and again after an interval of 3 to 4 weeks. Complement fixation tests (CFTs) were performed against the following antigens: influenza A, influenza B, adenovirus, psittacosis, coxiella, measles, respiratory syncytial virus (RSV), *Mycoplasma pneumoniae*, mumps, herpes zoster, herpes simplex, Coxsackie B, cytomegalovirus, and parainfluenza 1, 2, and 3. Antibodies to rubella were sought by haemagglutination inhibition. All convalescent sera were screened; acute phase sera were only tested if a titre of 1/20 or higher was obtained. Results were regarded as positive if there was at least a 4-fold rise in titre between acute and convalescent sera.

The interferon activity of serum collected within 2 hours of admission was assayed by a plaque inhibition technique, on a semimicro scale, using continuous vervet monkey kidney cells in wells in plastic (Matthews and Lawrence, 1979). The serum was diluted 1:10 and left on the cell sheet for 24 hours at 37°C in a humid atmosphere containing 5% carbon dioxide. The monolayers were washed and vesicular stomatitis virus was added as the challenge virus.

A reduction of at least 50% in the mean plaque count was taken as indicating the presence of interferon. Dilutions of the MRC Research Standard B (69/19) for human interferon were included with each test, and 1 unit of this was found to give between 50 and 70% reduction.

Bacteriological methods. CSF was sent to the microbiology department for immediate microscopy and culture. Blood was incubated at 37°C in glucose broth and thioglycollate, subcultures were made aerobically and anaerobically. Throat swabs were taken on serum-coated wool buds. In the first part of the study they were transported in Stewart's medium and plated within 4 hours. From July 1977 all throat swabs were taken by the same clinician, who plated them immediately on to blood and chocolate agar. Colonies were identified by standard techniques and all β-haemolytic streptococci were grouped serologically. Urine specimens were inoculated on to CLED medium within 4 hours of collection. Colonies were enumerated and identified by standard techniques. A significant growth was taken as $>10^8$ organisms/litre. Fresh stool specimens were plated on to deoxycholate agar and MacConkey agar and inoculated into selenite broth. Enteropathogenic *Escherichia coli* were identified by using antisera to 15 recognised enteropathogenic types (PHL Colindale). From April 1977 a selective medium was used to isolate campylobacter species (Skirrow, 1977).

Additional tests were WBC of the peripheral blood, plasma glucose level, and CSF protein and glucose concentrations.

Results

37 boys and 36 girls were studied. The mean age was 18·9 months and only 3 (4%) children were over 3 years. Two children were excluded because virological investigation had been omitted; one had meningitis, with *Haemophilus influenzae* cultured from the blood and CSF; the other child had clinical measles. All other patients admitted during the study period were retained, although a complete set of microbiological specimens was not obtained from every patient; there was sometimes insufficient serum for interferon assay and a few patients did not return for convalescent serology.

Virology results. A virus was identified from at least one site in 46 (63%) out of 73 patients. The viruses are named in Table 1; from 9 patients, viruses of more than one type were identified.

There was a significant rise in antibody titre in 14 (20%) out of 69 patients. All had a 4-fold response

Table 1 *Results of virus isolation tests with clinical diagnoses. (Number of patients in parentheses)*

Type of virus	*Clinical diagnosis*
Enterovirus (17):	
Echovirus (5) type 3 (3), 5 (1), 22 (1)	Tonsillitis (1), pharyngitis (1), otitis media (1), URTI (1), PUO (1)
Coxsackie A (7) type 2 (1), 4 (1), 10 (5)	Tonsillitis (2), pharyngitis (2), URTI with conjunctivitis (1), measles (1), PUO (1)
Coxsackie B (3) type 1 (1), 2 (1), 3 (1)	Pharyngitis (1), PUO (1), gastroenteritis with orchitis (1)
Poliovirus type 3 (1)	Measles vaccine*
Enterovirus (EM only) (1)	Otitis media with gastroenteritis†
Adenovirus (22) type 1 (6), 2 (12), 3 (1), 5 (1) type 1 with 3 (1), CFT only (1)	Tonsillitis (4), pharyngitis (1), otitis media (9), URTI (3), tonsillitis with gastroenteritis (1), otitis with gastroenteritis† (1), URTI with gastroenteritis (1), dysentery (1)‡, meningitis (1)§
Influenza B (1)	URTI
Parainfluenza (7) type 1 (1), 2 (1), 3 (5)	Tonsillitis (2), pharyngitis (1), otitis media (1), croup with otitis (1), URTI (2)
Measles (3) Measles CFT (2)	Measles (4), measles vaccine (1)*
Respiratory syncytial virus (2) serology only	Measles (1), tonsillitis (1)
Rhinovirus (2)	URTI (1), meningitis§ (1)
Cytomegalovirus (4)	Tonsillitis (1), otitis media (3)
Rotavirus (EM only) (2)	Gastroenteritis (1), otitis media with gastroenteritis (1)†

*Case 39 (see Table 2), †Case 23, ‡Case 75 (see Table 3), §Case 59 (see Table 2).

except one, with doubling of an initially high titre; from 11 of these patients a virus of the same type was isolated by tissue culture. A rise in antibody titre to RSV was demonstrated in 2 cases, but the virus was not isolated; in addition one of these patients was shown to be infected with an adenovirus by CFT and culture, and the other also had a positive measles CFT.

Interferon was detected in the serum of 31 (47%) out of 66 patients. From 16 of these a virus was isolated; there was no other evidence of a viral illness for the remaining 15 patients.

63 (86%) out of 73 patients had some evidence of a viral illness when all the methods were considered together—that is tissue culture, electron microscopy, mouse inoculation, serology, and interferon assay.

Evidence of a systemic viral illness was demonstrated in 20 (27%) cases by isolating a virus from the CSF, blood, or urine. A virus was isolated from the CSF of 4 patients, from the blood of 12, and from the urine of 13 patients (Table 2).

Bacteriology results. Pathogenic bacteria were isolated from 21 (29%) patients, Table 3. There was no difference in the isolation rate when throat swabs were plated immediately rather than transported in Stewart's medium.

A systemic bacterial illness was demonstrated in 3 (4%) cases. From one patient *H. influenzae* was isolated from the blood and CSF. Two patients had a significant *E. coli* bacteriuria, which was confirmed on subsequent specimens. From 14 of the patients with a bacterial isolation a virus was also recovered.

Interferon was detected in 9 cases with a bacterial isolation but a virus was also recovered from 5 of these.

Other investigations. The patient with *H. influenzae* meningitis had a high CSF WBC and a high CSF protein level; of the rest only one patient had more than 4/mm^3 white cells in the CSF, and one had a CSF protein $>0{\cdot}4$ g/l (40 mg/100 ml). There was no relationship between the CSF findings and the nature of the pathogen, or evidence of viral dissemination.

The WBC did not distinguish those with bacterial isolations from those with viral isolations. However, a group of patients from whom adenoviruses were identified had significantly higher white cell counts than any others, i.e. 80% of patients with adenovirus isolations had >15 000/ml (mainly polymorphs) compared with 36% of patients without adenovirus ($\chi^2 = 9{\cdot}8$, $P<0{\cdot}01$).

Clinical data

From the histories given by the parents perinatal asphyxia may have occurred in 6 cases. Later in the first year of life one infant had an asphyxial episode but the others had an unremarkable medical history. The probability of normal developmental achievement before the convulsion was indicated by asking the mothers the ages at which their children had achieved four major milestones (Neligan and Prudham, 1969). 66 (90%) children had reached all four milestones by the ages expected for 90% of children of their own sex, and no child failed more than one milestone. Thus the developmental achievements of the group were no different from those of the general population. We therefore cannot verify that perinatal problems and abnormal development are commonly found in children suffering febrile convulsions (Millichap, 1968; Wallace, 1972, 1975). A parent or sibling of 8 (11%) of our children was known to have suffered from febrile convulsions and a further 6 (8%) had each suffered at least one convulsion which was not associated with fever.

The mean length of illness before the convulsion was 13·4 hours (range 0 to 96). The symptoms noted by the parents were nonspecific: irritability, anorexia, and fever were commonly recorded but cough, vomiting, or diarrhoea sometimes indicated the likely site of infection.

Table 2 *Details of patients with viruses isolated from CSF, blood, or urine*

Virus	*Case*	*CSF*	*Blood*	*Urine*	*Throat swab*	*Naso-pharyngeal secretions*	*Stool*	*Serology*	*Other viruses*	*Bacteria isolated*	*Clinical diagnosis*
Adenovirus type 1	20	–	+	+	+	0	–	–	–	–	Otitis media
Adenovirus type 1	27	+	–	+	–	0	–	Adenovirus	–	Urine *E. coli*	Otitis media
Adenovirus type 1	56	–	–	+	+	–	+	–	–	–	Otitis media
Adenovirus type 1	59	+	+	–	+	–	–	–	NPS rhinovirus	CSF and blood *H. influenzae*	Meningitis
Adenovirus type 3		–	–	+	+	+	–	–			
Adenovirus type 2	7	–	+	–	+	0	+	Adenovirus persistent high titre	–	–	Otitis media
Adenovirus type 2	8	+	–	–	–	0	–	Adenovirus	–	–	URTI
Adenovirus type 2	13	–	–	+	+	0	+	–	–	–	Tonsillitis
Adenovirus type 2	44	–	–	+	+	0	–	Adenovirus	–	Throat. Haemophilus	Otitis media
Adenovirus type 2	67	–	+	–	+	+	(+EM) +	Adenovirus	–	–	Tonsillitis
Echo type 3	63	–	+	–	+	–	+	–	–	Throat. *Streptococcus pneumoniae*	URTI
Echo type 3	71	–	+	+	+	0	0	–	–	–	PUO
Coxsackie A10	50	–	+	–	–	0	+	–	–	–	Pharyngitis
Coxsackie B2	61	–	+	+	+	+	0	–	–	Throat. Haemophilus	Pharyngitis
Coxsackie B3	46	–	+	+	+	+	+	–	–	Throat. Haemophilus	PUO
Parainfluenza type 2	9	–	+	–	+	0	–	Paraflu type 2	–	Throat. Streptococcus G	Croup
Parainfluenza type 3	72	+	–	+	–	+	0	–	–	–	Pharyngitis
Measles	38	–	–	+	+	+	0	Measles	–	–	Measles
Measles	39	–	+	–	–	–	–	Measles	Stool polio type 3	–	Measles vaccine
Measles	70	–	+	+	+	+	–	Measles	–	–	Measles
Cytomegalovirus	6	–	–	+	–	0	–	–	–	–	Tonsillitis
Totals	20	4	12	13							

+ Virus isolated, – no virus isolated, 0 no specimen taken.
URTI = upper respiratory tract infection, PUO = pyrexia of unknown origin, NPS = nasopharyngeal secretions.

The mean rectal temperature recorded immediately after admission was 39·5°C and ranged from 37·5 to 42°C. 11 (15%) children had received at least one dose of an antibiotic before collection of specimens for microbiology.

The clinical diagnoses of the precipitating illnesses were classified according to the guidelines suggested by Court (1973). An upper respiratory tract infection (URTI) was further described as coryza, tonsillitis, pharyngitis, or otitis media if the predominant symptoms or signs were localised to the nose, tonsils, pharynx, or tympanic membranes respectively. In Tables 1, 2, and 3 the diagnoses are tabulated against the pathogens which were subsequently identified. A morbilliform or maculopapular rash was reported during the illness of 14 patients, and pathogens identified from these cases are listed in Table 4. No pathogens were found in 18 patients whose diagnoses were tonsillitis (1), pharyngitis (2), otitis media (3), coryza (1), URTI (7), gastroenteritis (2), gastroenteritis with URTI (1), and pyrexia of unknown origin (1).

Upper respiratory illnesses were found in 59 (81%) of all patients and gastrointestinal illnesses in 9 (12%). These figures are close to those recorded in other surveys (Millichap, 1968).

49 (67%) patients had had fits each one lasting under 15 minutes, which was not followed by further fits in the same illness, and was not accompanied by localising signs. These were classified as 'simple fits'. One or more 'complex' features occurred in the remaining 24 (33%) patients. Eight patients had fits which each lasted longer than 15 minutes (but only 2 convulsed for longer than 30 minutes). 10 patients had more than one convulsion in the same illness, and 5 patients had localising features or a

Table 3 *Results of bacteriology with clinical diagnoses. (Number of patients in parentheses)*

Site	*Organism*	*Diagnosis*
Throat (16)	Streptococcus group A (1)	Tonsillitis (1)
	Streptococcus group G (1)	Otitis media (1)
	S. pneumoniae (3)	Tonsillitis (1), URTI (1), influenza (1)
	Haemophilus species (10)	Tonsillitis (1), pharyngitis (1), otitis media (3), URTI (3), gastroenteritis with orchitis (1)* PUO (1)
	Streptococcus G. with Haemophilus (1)	Otitis media (1)
Stool (2)	*Shigella sonnei* (1)	Dysentery (1)**
	E. coli O111 (1)	Otitis media† (1)
Blood with CSF (1)	*H. influenzae*	Meningitis‡
Urine (2)	*E. coli* (2)	SBE (1), otitis media§ (1)

*Coxsackie B1 also isolated (throat and stool), **adenovirus 2 (stool) also isolated (see Table 1), †CMV (throat) and echo 5 (stool) also isolated, ‡Case 59 (see Table 2), §Case 27 (see Table 2).
SBE = Subacute bacterial endocarditis.

Table 4 *Virological findings in 14 patients with rashes. (Number of patients in parentheses)*

Echovirus type 3 (1)
Coxsackie A10 (1)
Adenovirus type 2 (2); type 3 (1)
Cytomegalovirus (1)
Measles (2)
Measles CFT with respiratory syncytial virus CFT (1)
Cytomegalovirus with echovirus type 5 (1)
Adenovirus type 1 with parainfluenza type 3 and Coxsackie A10 (1)
Parainfluenza type 3 with Coxsackie A10 (1)
Coxsackie A4 with measles CFT (1)
No virus (1)

subsequent hemiparesis, but none had signs which persisted for longer than 24 hours. Six patients stopped convulsing only after they had been given parenteral anticonvulsants in hospital.

Patients with 'complex' convulsions had a similar spectrum of viral and bacterial findings as those with 'simple' convulsions, and the same incidence of blood and urine viral isolations. Convulsions had 'complex' features in 2 of the 4 patients carrying a

Table 5a *Comparison of findings in febrile convulsions and gastroenteritis: virology results*

Type of virus	*Throat swab isolations*		*Stool isolations—tissue culture*		*Stool electron microscopy*	
	Febrile convulsions (71 patients)	*Gastroenteritis (125 patients)*	*Febrile convulsions (62 patients)*	*Gastroenteritis (150 patients)*	*Febrile convulsions (62 patients)*	*Gastroenteritis (150 patients)*
Adenovirus	12 (17)*	4 (3)*	12 (19)	17 (11)	2 (3)	3 (2)
Enterovirus	6 (9)	2 (2)	5 (8)	12 (8)	2 (3)	3 (2)
Parainfluenza	3 (4)	1 (1)				
Cytomegalovirus	4 (6)	5 (4)				
Influenza	1 (1)	0				
Measles	2 (3)	0				
Respiratory synctial virus	0	1 (1)				
Rhinovirus	1 (1)	3 (2)				
Herpes simplex	0	1 (1)				
Rotavirus					2 (3)*	76 (51)*
Calici, corona, or astrovirus					0	4 (3)
Totals	29 (41)*	17 (14)*	17 (27)	29 (19)	6 (10)*	86 (57)*

*$P<0 \cdot 01$ by χ^2 test.
Percentages are given in parentheses.

Table 5b *Comparison of findings in febrile convulsions and gastroenteritis: bacteriology results*

Pathogenic bacteria	*Throat swab isolations*		*Pathogenic bacteria*	*Stool isolations*	
	Febrile convulsions (70 patients)	*Gastroenteritis (135 patients)*		*Febrile convulsions (67 patients)*	*Gastroenteritis (150 patients)*
Streptococcus group A	1 (1)	3 (2)	*E. coli* (enteropathic)	1 (1)	2 (1)
Other haemolytic streptococci	1 (1)	7 (5)	Shigella	1 (1)	8 (5)
			Salmonella	0	11 (7)
S. pneumoniae	3 (4)	4 (3)	Campylobacter	0	5 (3)
Haemophilus species	10 (14)	8 (6)			
Streptococcius group G with Haemophilus	1 (1)				
Totals	16 (23)	22 (16)		2 (3)*	26 (17)*

*$P<0 \cdot 01$ by χ^2 test.
Percentages are given in parentheses.

virus in the CSF but one of these (Case 59) had *H. influenzae* meningitis (Table 2).

No relationship was found between 'complex' features and the WBC of the CSF or blood or the temperatures recorded after admission.

Microbiological findings in gastroenteritis

A concurrent but separate study of gastroenteritis comprised 150 children whose ages were similar to those with febrile convulsions (Lewis *et al.*, 1979). Both projects were undertaken by the same people and microbiological methods were identical. Viral and bacterial cultures were taken from stools and throat swabs, and stools were examined for rotavirus by electron microscopy. CSF, blood, and urine were not collected, nor were mouse inoculation tests performed.

The two groups of patients are compared in Table 5. Significantly more patients with febrile convulsions carried viruses in their throats. In gastroenteritis, rotavirus was by far the most common pathogen and bacterial pathogens were more often identified in the stool.

Discussion

The results indicate that common viruses can invade the blood stream and CSF and, presumably, the central nervous system. We suggest that systemic invasion occurred in all cases and was important in producing both fever and convulsion. We failed to isolate a virus from all specimens of blood and CSF because we took very small (1 ml) quantities, and we suspect that the virus was rapidly eliminated from these sites as the child recovered from the convulsion.

The study has shown a viral aetiology in a higher proportion of patients than others have reported (Wallace and Zealley, 1970; Familusi *et al.*, 1972; Stokes *et al.*, 1977), probably because several methods of viral diagnosis were used. Tissue culture from fresh specimens gave the highest number of positive results, and additional viruses were detected by electron microscopical examination and inoculation of suckling mice. Complement fixation tests were rarely positive, but we did not seek an immune response further by titrating neutralising antibody against the specific viruses cultured. Interferon assay was an indication of viral illness rather than definitive diagnosis. We detected interferon in the serum of 16 (36%) out of 45 patients from whom a virus was identified by tissue culture or serology, but we also found interferon in 15 patients from whom no virus was isolated. A previous study from this unit detected interferon in the acute phase serum of 17 (38%) out of 45 children and adults with a proved virus infection, but from none of 25 with bacterial, mycoplasma, or rickettsial infections, or from 61 healthy persons (Matthews and Lawrence, 1979). We suggest that a virus was present but not demonstrated in our 15 patients with interferon but no other evidence of viral infection. This is not an unreasonable assumption as we did not perform tests for a number of viruses, including EB virus and hepatitis viruses.

We cannot prove that the viruses we identified were responsible for the illnesses which precipitated the convulsions, but we have good supportive evidence.

Firstly, a virus of the same type was often isolated from multiple sites in the same patient, and there was no cross contamination. The complement fixation tests often (but not always) corroborated the findings.

Secondly, the clinical features associated with the viruses agree well with those described in reports (Tables 1, 2, and 3). Thus, the adenoviruses and the parainfluenza viruses were particularly associated with tonsillitis and otitis media (Medical Research Council, 1965; Gardner, 1968; Clarke, 1973; Pereira, 1973). Diarrhoea was associated with rotavirus and with adenoviruses (Du Pont *et al.*, 1977; Walker-Smith, 1978). Rashes were observed with measles virus and Coxsackie A viruses (Table 4). Coxsackie B1 was identified in the stool and throat swab of a patient who had gastroenteritis followed by orchitis, and an enterovirus was found in 3 out of 4 children for whom pyrexia of unknown origin was the only diagnosis (Dalldorf and Melnick, 1965; Melnick, 1965; McLean, 1966). Four patients were immunised in the 2 weeks before their convulsions, but in 2 (DTP and polio vaccines) viruses were isolated which were possibly of more significance than the vaccine in precipitating the convulsion; in the third case cholera vaccine was given 1½ hours before the temperature suddenly rose with a convulsion and an unusually severe local inflammatory response. In the fourth case measles virus was isolated from the blood of a child who had measles vaccine 10 days before the convulsion. We have seen no other documented case of measles viraemia attributed to the febrile reaction to immunisation (Landrigan and Witte, 1973).

The different pattern of viruses identified in children with gastroenteritis adds further support to the validity of our findings (Table 5). Rotavirus has always been associated with diarrhoea, but adenoviruses and enteroviruses could be responsible for either respiratory or gastrointestinal illness, depending on their site of maximal multiplication (Dalldorf and Melnick, 1965; Ginsberg and Dingle, 1965; Melnick, 1965; Pereira, 1973; Steinhoff, 1978). Of doubtful significance were bacterial pathogens in throat swabs, which were isolated with similar frequency in gastroenteritis and febrile convulsions, and have been commonly found in the throats of healthy young children (Masters *et al.*, 1958; Gardner, 1968). Although many children with febrile convulsions had clinical tonsillitis, a haemolytic streptococcus group A was isolated from only one throat.

We have implicated a systemic viral illness in the majority of febrile convulsions, but a generalised bacterial illness was possible in 3 (4%) cases where a bacterial pathogen was isolated from the CSF, blood, or urine (Table 3). The first child (Case 59) had clinical meningitis attributed to *H. influenzae*; we cannot explain the significance of finding two types of adenovirus in the CSF, blood, throat, and urine of this patient (Table 2). The second child had *E. coli* bacteriuria, but *E. coli* in a subsequent blood culture confirmed a diagnosis of bacterial endocarditis. The third patient (Table 2, Case 27) had significant but asymptomatic bacteriuria with clinical otitis media; an adenovirus was isolated from the CSF and urine, and there was a rising CFT titre to adenovirus.

We investigated only those with convulsions but transient viraemia or bacteraemia may occur in other children during acute febrile illnesses. We suggest that a convulsion occurs when a child with a predisposition to febrile convulsions is exposed to a systemic virus or bacterium at an age when the immature brain is susceptible (Coyle, 1976; Ounsted, 1976b). We had evidence of no predisposing factors except family history. After one year the occurrence of subsequent febrile convulsions in our cohort bears no relationship to the nature or site of the pathogen in the initial episode.

It has recently been shown (Stephenson, 1978) that not all febrile convulsions are classical epileptic paroxysms but some may be related to vagal reflexes. We may therefore have studied the microbiology of a heterogeneous group of central nervous system phenomena described as 'febrile convulsions'. We hope that more thorough virological investigations will be undertaken in conjunction with electrophysiology, immunology, and epidemiology to show how viruses can affect the central nervous system in different ways, ranging from a brief convulsion to a florid encephalitis or to a slow virus illness such as subacute sclerosing panencephalitis.

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Family resemblances of height, weight, and body fatness

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SUMMARY In a study of 256 families, among whom were twins, midparent-adult *son* correlations for height, weight, and combined skinfold measurements were 0·67, 0·47, and 0·23 respectively. The corresponding midparent-adult *daughter* correlations were 0·63, 0·42, and 0·24. Midparent-growing offspring correlations were highest for height, less for weight, and insignificant for combined skinfold measurements. These data and the resemblances found between twins and siblings led us to conclude that there is a significant genetic contribution to the variation of height and weight, but that body fatness appears largely to be determined by environmental factors.

Twin studies have suggested body fatness in childhood to be largely genetically determined (Brook *et al.*, 1975; Börjeson, 1976). Parent-growing offspring correlations for skinfold measurements, however, have been found to be low (Garn and Clark, 1976; Mueller and Titcomb, 1977) and to be of similar value to parent-adopted child skinfold correlations (Garn *et al.*, 1976). As body fatness may be influenced by environmental factors—for example exercise and diet (Parizkova, 1963; Sims *et al.*, 1968), resemblances between relatives may, more than anything else, reflect their shared common environments.

In this study, correlation coefficients of body fatness between various family members have been calculated and compared with correlations found for weight and height, the last being generally considered to be largely genetically determined (Pearson and Lee, 1903).

Materials and methods

Between 1961 and 1962, the heights and weights of parents and offspring and the skinfold measurements of offspring aged 2 to 15 were recorded for 330 families (Huntley, 1966). An attempt was made to trace these families, among whom were twins. Heights, weights, and skinfold measurements were recorded on parents and offspring. Heights were measured on a Holtain portable stadiometer, weights on beam scales (the subjects wearing underclothes only), and skinfolds with Holtain calipers at the triceps, biceps, subscapular, and suprailiac sites (Weiner and Lourie, 1969).

The distribution of the skinfold measurements was logarithmic. Log transformation of the data normalised the distribution (Edwards *et al.*, 1955). Log-transformed data were used in the analysis.

The sum of the 4 skinfold measurements was used to indicate body fatness (Parizkova, 1961; Durnin and Womersley, 1974). As skinfold measurements change with age, and as the subjects were measured at widely different ages, standard deviation (SD) scores for the combined measurements of each individual were calculated. The means and SDs against which each individual was compared were the means and SDs for that individual's year group, calculated from the study population.

Weights of adult offspring were compared with the earlier weights of their parents recorded between 1961 and 1962. Heights were compared directly between adult offspring and their parents. Skinfold thickness SD scores were used to compare skinfold thicknesses between offspring and parents.

Results

296 (89%) of the families were traced and 256 (78%) remeasured. The mean heights and weights of the parents and of the offspring, now aged at least 20 years, are shown in Table 1.

Parent-adult offspring correlations of height, weight, and skinfold thickness are shown in Table 2. The relationships between the anthropometric

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measurements in the parents and in their growing children varied from age to age. The yearly figures are available on request from the authors: values for parent-growing offspring correlations were highest for height, less for weight, and insignificant for skinfold thickness.

Table 1 *Heights and weights (mean ± SD) of adult offspring and their parents*

	Height (cm)	*Weight (kg)*	*Mean age at time of measurement*
Fathers (n = 186)	172·4 ± 0·52	73·7 ± 0·79	42·2
Mothers (n = 211)	162·9 ± 0·40	62·3 ± 0·53	39·7
Sons (n = 345)	177·5 ± 0·38	69·2 ± 0·57	25·2
Daughters (n = 341)	164·1 ± 0·33	57·6 ± 0·48	24·9

Table 2 *Parent-adult offspring correlations of height, weight, and skinfold thicknesses*

	Height		*Weight*		*Combined skinfolds*	
	r	*n*	*r*	*n*	*r*	*n*
Midparent-son	0·67	302	0·47	302	0·23	238
Midparent-daughter	0·63	287	0·42	257	0·24	228
Father-son	0·57	316	0·30	316	0·19	264
Father-daughter	0·54	264	0·33	264	0·10	257
Mother-son	0·59	332	0·37	332	0·21	311
Mother-daughter	0·46	309	0·34	309	0·20	250

Table 3 *Resemblances of anthropometric measurements between twins in adult life and in childhood*

	Monozygotic twins		*Dizygotic twins*	
	Male	*Female*	*Male/male*	*Female/female*
No. of pairs	29	20	46	45
Adult				
Heights	0·94	0·86	0·57	0·37
Weights	0·85	0·77	0·43	0·51
Combined skinfolds	0·74	0·81	0·68	0·16
In childhood				
Heights	0·95	0·99	0·95	0·95
Weights	0·99	0·99	0·88	0·79
Combined skinfolds	0·81	0·81	0·48	0·51

Table 4 *Resemblances between siblings for combined skinfold measurements*

	Childhood	*Adult*
One in each pair a twin		
Brother-brother	0·34 (68)	0·36 (60)
Sister-sister	0·19 (38)	−0·03 (48)
Neither in pair a twin		
Brother-brother	0·20 (15)	0·30 (25)
Sister-sister	0·34 (13)	0·05 (20)

Analyses of the twin data in childhood and in adult life are shown in Table 3. Resemblances between siblings for combined skinfold measurements in childhood and in adult life are shown in Table 4.

Discussion

The secular trend in height is clearly shown in Table 1. The individual parent-offspring correlations (Table 2), which come close to those anticipated by Fisher (1918) for fully genetically determined characteristics, indicate that adult height is largely genetically determined. For such a characteristic, the regression coefficients of offspring on midparent (1·0) and midparent on offspring (0·5) will give a correlation coefficient of 0·71. Our data show values which approach this and agree with previously published figures (Brook *et al.*, 1977).

The skinfold measurements, by contrast, showed no such pattern. No resemblances were found between parents and their offspring, either as children or as adults. Sisters did not resemble one another and brothers only slightly. There is little suggestion of any genetic contribution to body fatness levels from these data.

On the other hand, correlations of skinfold thicknesses between twins in childhood taken on their own suggest a very considerable genetic contribution to the variation in skinfold measurements. The adult values were different: while monozygotic twins continued to resemble each another closely, the male dizygotic twins resembled one another more than had been the case in childhood and the female dizygotic twins showed no resemblance at all.

The parents' skinfold measurements were not taken in the first study and at the time of the second one about three-quarters of the offspring no longer lived at home. All the parent-growing offspring skinfold correlations and most of the parent-adult offspring skinfold correlations therefore reflect the fact that parents and offspring were not sharing common family environments. The lack of resemblances found in this study compared with the positive correlations found in others between parents and offspring when the offspring were still living at home (Garn and Clark, 1976; Mueller and Titcomb, 1977), suggests common family environment to be the important factor in the determination of body fatness, which the twin data do not negate.

The use of differences between monozygotic and dizygotic twins to assess the relative importance of genetic and environmental contributions to the determination of the variation of a characteristic depends upon the assumption that twins are treated more or less similarly whether they are identical or nonidentical. Smith (1965) noted many more similarities in environmental factors between identical twins in childhood compared with nonidentical twins. Twins who look alike were treated alike. Consequently, for a characteristic largely environmentally determined, it could be anticipated that identical twins would resemble each other more in childhood than nonidentical twins.

In collecting data from the adult twins, an attempt was made to assess activity levels. There were too many variables for satisfactory statistical analysis, but an extraordinary similarity in lifestyles and habits was noted between the identical twins. The male nonidentical twins also shared much in common and took advantage of having a brother of the same age with whom to share sporting interests. The nonidentical female twins, on the other hand, showed little in common. The resemblances in body fatness between the adult twins reflected these differences and the lack of resemblance with their singleton brothers and sisters was conspicuous.

The results for body weight lay between those for height and skinfold measurements, as would be anticipated, as weight includes both. The correlations more closely resembled the findings for height, probably because there were few obese subjects in the study group. All our analyses confirmed the widely held view that weight is conspicuously unreliable as a measure of body fatness.

Genetic factors play a large part in the determination of adult height; environmental factors largely determine adult body fatness levels. Figures derived from twin data alone should be regarded with a considerable degree of suspicion.

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Ethnic differences in the Goodenough–Harris draw-a-man and draw-a-woman tests

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SUMMARY The draw-a-man (DAM) and draw-a-woman (DAW) tests were given to 307 schoolchildren in Petaling Jaya, Malaysia. The children were ethnically Malay, Chinese, or Indian (Tamil), and all came from lower socioeconomic groups. The standard scores of the Chinese children averaged 118 in the DAM and 112 in the DAW tests. These scores were significantly better than the American standards. Malay children scored significantly lower than Chinese, and Tamil children scored lower again. The nutritional status of the children had no influence on the scores. Chinese and Tamil children scored better in the DAM than the DAW, while in Malay boys the reverse was true. Malay children tended to emphasise clothing in the DAM, but Chinese and Tamil children scored better on items relating to facial features and body proportions. The Goodenough–Harris draw-a-person tests are obviously not culture-free, but the causes of ethnic differences have not been elucidated.

A child's performance in an intelligence test depends on his cultural background, his genetic intellectual potential, and his motivation. Most tests have been designed to match the cultural background of middle-class American or Western European children and cannot safely be used with other groups. However, one test which has the potential of being truly cross-cultural is the Goodenough–Harris draw-a-person test. The human form is universally available as a model, and figure drawing is common among children of all ethnic groups. We used this test on groups of schoolchildren from similar socioeconomic levels but very different cultural backgrounds to try to find whether significant variability existed.

Methods

Malaysia is particularly suited for cross-cultural studies. In the cities, there are peoples of Malay, Chinese, and Indian backgrounds living side by side, but still retaining their own vernacular and customs. Within each ethnic group, the families range from affluent to very poor, and nutritional levels also vary widely. Children from poorer families usually attend vernacular schools intermittently and leave early.

There were data on 307 children, although not all information was available for some. The data used in this study were (1) Age; this was obtained from birth certificates and ranged from 6½ to 10½ years. (2) Sex of the child. (3) Ethnic group; there was no intermarriage or ethnic mixing among the groups studied. (4) Type of school. Malay and Indian children were taught in their vernacular language, Malay and Tamil respectively. Chinese children attending Chinese language schools were taught in Mandarin, although their vernacular languages were generally Cantonese or Hokkien. (5) Number of children currently at home. (6) Family income; this was obtained by questioning the parents. (7) Number of years' schooling of each parent. (8) Height and weight of the child. This was converted to a percentage of the Stuart and Stevenson standard for a child of that age and sex (Nelson, 1964). (9) The Goodenough–Harris draw-a-man (DAM) and draw-a-woman (DAW) tests; these were done in the school classrooms, and raw scores were converted to standard scores using the tables given by Harris (1963).

The children whose drawings have been used in this study were all attending government primary

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schools in Petaling Jaya, a satellite city of Kuala Lumpur, the capital of Malaysia. These schools are free and, because at the time of the study most teaching was done in vernacular language, each school had predominantly pupils from one ethnic group (for further details see Dugdale and Chen, 1977).

Medical students doing their paediatric posting in the University of Malaya ran a School Health Service under the supervision of S.T.C. Children were seen class by class by the medical students. The DAM and DAW tests were done in the classroom by the whole class.

Because the child's name appeared on his drawings, it was not possible to score the test 'blind'. However, the scoring method was objective and standardised, so knowledge of the race of the child should have had little or no effect on the scoring.

Results

Overall scores in the DAM test. The mean values of the standard scores in the DAM and DAW tests are shown in Table 1. The scores are standardised on American children to have a mean of 100 and a SD of 15 points. The distribution of the DAM scores is shown in Fig. 1.

When compared with expected American standard scores, the Chinese children, boys and girls, scored higher (Kolmogorov-Smirnov 2-sample test, $P < 0{\cdot}01$) than American standards, but Chinese boys and girls did not differ significantly one from the other. On the other hand, Tamil children scored lower than American standards ($P < 0{\cdot}05$) and again boys did not differ from girls. Among Malay children, neither boys nor girls differed from one another or from American standards, although in Malay girls the higher mean score approached the level of significance ($0{\cdot}1 > P > 0{\cdot}05$). Within the three ethnic groups Chinese children scored higher than Malays ($0{\cdot}05 > P > 0{\cdot}025$), who in turn scored higher than the Tamil children ($0{\cdot}05 > P > 0{\cdot}025$). A few Tamil children drew men in long robes (see Fig. 3c) which would detract from the score. However, even allowing for this, Tamil children scored badly.

Table 1 *Numbers of children in each group who completed the DAM and DAW tests, with the mean standard scores*

Group	*Test*			
	Draw-a-man		*Draw-a-woman*	
	No.	*Mean score*	*No.*	*Mean score*
Malay				
Boys	13	102·0	13	106·8
Girls	29	111·9	29	115·17
Chinese				
Boys	57	116·2	57	110·1
Girls	64	120·6	64	114·1
Tamil				
Boys	65	96·6	64	91.5
Girls	79	96·4	77	94·6

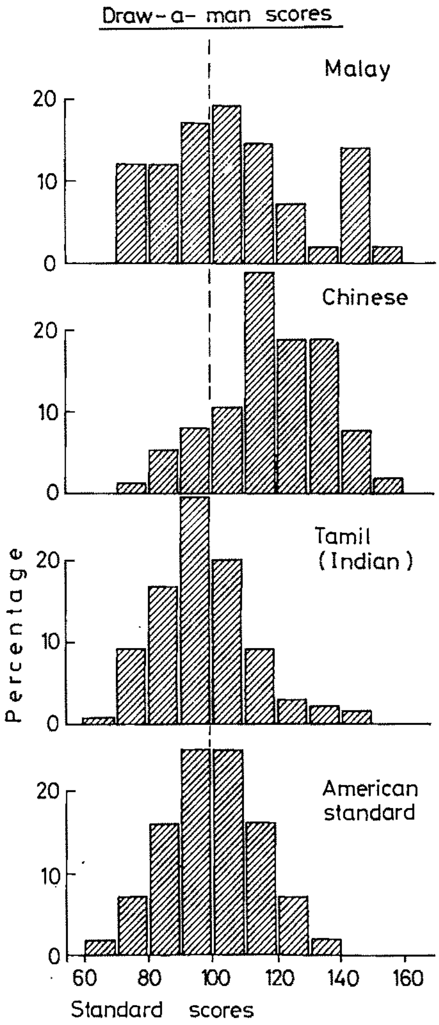


Fig. 1 *Distributions of scores in the DAM test in children of different ethnic groups. American standard score is shown at the bottom.*

Overall scores in DAW test. The mean scores are shown in Table 1 and the distributions are shown in Fig. 2.

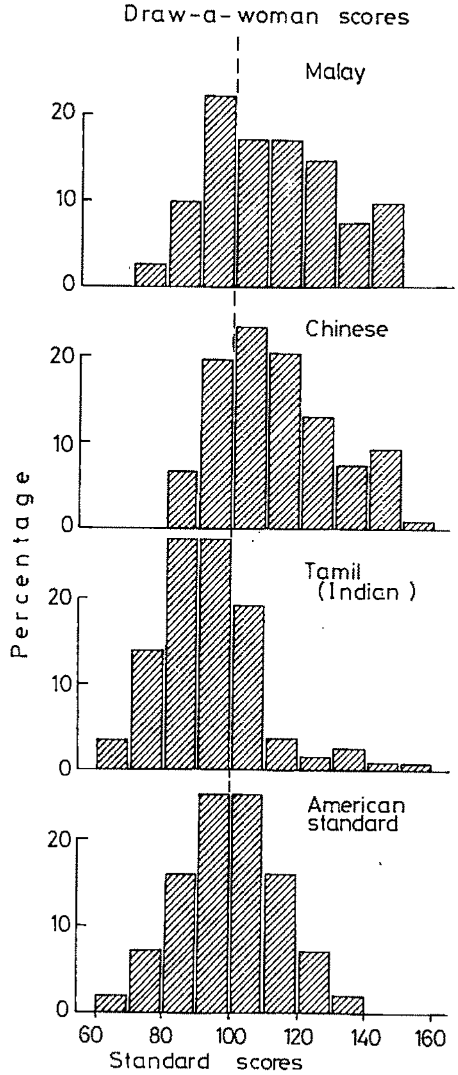


Fig. 2 *Distributions of scores in the DAW test. American standard score is shown at the bottom.*

Within each ethnic group, there were no significant differences between boys and girls. As with the DAM test, Chinese children scored higher than the American standards (P<0·01) and Tamil children lower (P<0·01) while Malay children tended to be better, but this did not quite reach the P = 0·05 level of significance. There were no significant differences between Malay and Chinese children, but these two groups had much higher scores than Tamil children (P<0·001).

Effects of nutrition and other environmental factors on scores. Because of the high correlation (r = 0·80) between DAM and DAW scores the mean value of the DAM and DAW was used as the dependent variable in the analysis. Multiple regression analysis was performed using the percentage present weight-for-age of the child as an indicator of nutritional status, family size, family income, and educational achievement of the parents as independent variables. These data were available on 263 children. Only 18% of the variance in the DAM and DAW scores was accounted for by these factors, and family income was the only significant single factor. Further testing with the extended median test showed that sex of the child had no effect on the scores. Although all children came from poor families, the Chinese families had slightly higher monthly incomes than the Malays, who again had slightly higher incomes than Indians. The DAM and DAW scores were recalculated to make allowance for these variations in income, but the statistically significant differences in the scores were unchanged. It is interesting that the current nutritional status of the child did not affect the score.

Relationship between DAM and DAW scores. An interesting pattern was found in the levels of the DAM and DAW scores among children of different ethnic groups (Table 2).

Among the Chinese children, both boys and girls scored significantly higher in the DAM than in the DAW test. A similar result was found in Tamil children. However, Malay boys scored better in the DAW than the DAM (P ≃ 0·02) and Malay girls showed no significant difference between the two tests.

Differences in patterns of drawing. Apart from diversity in overall scores, children from various

Table 2 *Pattern of scoring in the DAM and DAW. Numbers in each group were treated using χ^2 against the hypothesis that the two patterns of scoring should be equal. Children with tied scores are omitted.*

Group	*No. of children with each pattern of scoring*		*Statistical significance P*
	DAM>DAW	*DAM<DAW*	
Malay			
Boys	2	10	<0·05
Girls	15	13	NS
Chinese			
Boys	36	19	<0·05
Girls	47	15	<0·001
Tamil			
Boys	46	16	<0·01
Girls	53	24	<0·001

ethnic groups tended to emphasise different features of their drawings. We examined this by analysing the 73 individual items of the DAM score. For children in each ethnic group the items have been ranked in order of decreasing frequency of scoring. That is, an item which was scored positive in every child is ranked first, and items in which no child scored are ranked last. The rankings obtained for the three groups of children were compared, and items showing wide variation in ranking noted. In this way different patterns of drawing could be detected without interference of the variation in total scores. There were 7 items where the difference in rankings among the three groups was $\geqslant 20$ (items 15, 18, 19, 22, 23, 38, and 52) and a further 9 where the rank differences were $\geqslant 15$ (items 13, 29, 48, 50, 55, 56, 58, 59, and 62). When these differences were tabulated a distinct pattern emerged (Table 3).

Table 3 *Pattern of scoring of individual items in the DAM*

Group of children	*Less commonly found features*	*More commonly found features*
Malay	23 Proportion and position of ears	55 Clothing I
	62 All body parts in proportion	56 Clothing II
	18 Hair I	58 Clothing IV
	19 Hair II	59 Clothing V
	22 Ears shown	52 Tapering of arms
Chinese		15 Projection of chin
		29 Wrist and ankle shown
		50 Proportions of face
Indian	55 Clothing I	38 Knee shown
		22 Ears shown
		13 Nose and lips in two dimensions
		48 Proportions of head

The most striking differences were among the Malay children who tended to score well on clothing and poorly on body proportions and facial features. Indian (Tamil) and Chinese children tended to emphasise facial features and there may be a tendency for Tamil children to score poorly on items related to clothing. The various items in the scoring system are not independent, so statistical tests could not be used to find the significance of these patterns. Examples of drawings showing these differences are shown in Fig. 3a, b, c.

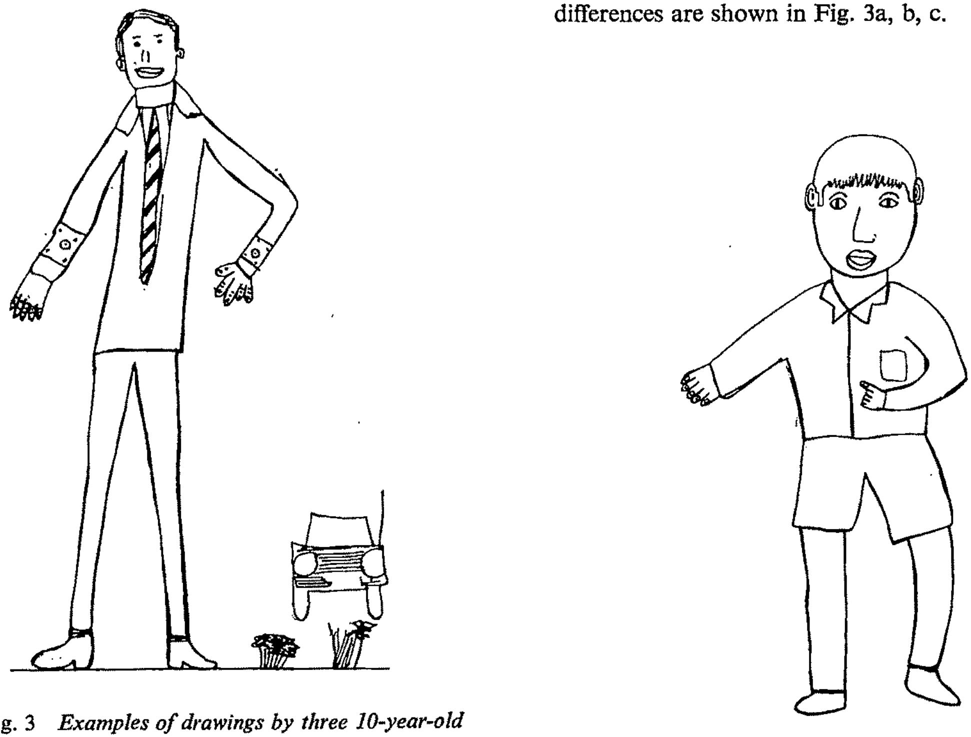
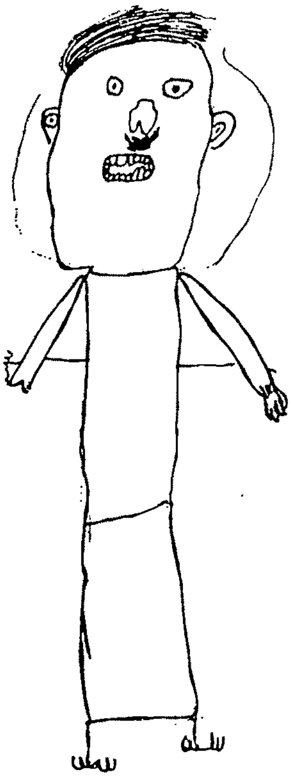


Fig. 3 *Examples of drawings by three 10-year-old children of different ethnic groups.*

(a) *The picture of a man by a Malay child emphasises the clothing. Note also the car in the background. (IQ equivalent 105).*

(b) *Chinese child has drawn a man with very simple clothing but excellent facial features. (IQ equivalent 124).*



(c) *Tamil child has drawn a less satisfactory man; even allowing for the long robe which is worn by some Indian men.* (*IQ equivalent 79*).

These drawings have been copied by an artist, as the original pencil drawings did not reproduce photographically.

Discussion

Although drawings of the human figure appear to be a valid measure of a child's growth in conceptual complexity (Harris, 1963), there must also be some effects of cultural influences and personality characteristics. This study confirms the work of Sundberg and Ballinger (1968) and of earlier authors in showing that there are influences which invalidate the draw-a-person as a culture-free test. The standard scores for the DAM and DAW tests were lowest in the Tamil children and these differences could not be accounted for by the measured nutritional or social factors. All such measures must be incomplete and the fact that no causative factors have been identified does not mean that they do not exist. It would certainly be important to find why Chinese children from poor socioeconomic backgrounds score so much better than American children on whom the tests were standardised.

Although the factors influencing the scores cannot be identified, there is ample evidence that they exist and differ among the three ethnic groups we studied. The evidence takes two main forms. When the DAM and DAW scores are compared in individual children, more Chinese and Tamil children scored better in the DAM than the DAW. It is possible that the Tamil children were disadvantaged in the DAW as the customary ethnic female dress, the sari, does not promote good scoring in the DAW, but this could not apply to the Chinese children. Nor does it explain why Malay girls showed no difference between DAM and DAW, but Malay boys scored higher in the DAW than the DAM.

The other feature of the DAM is the different features emphasised by the children of different ethnic groups. Malay children tended to score higher on items related to clothing, while Chinese and Tamil children were apparently more aware of facial features and body proportions. It is possible that the response of Malay children was influenced by the traditional Muslim prohibition on portraits of human subjects, even though this prohibition is by no means rigidly observed.

Any speculation about the causes of the differences in overall scores or in the patterns of response would be unwise in view of the lack of factual data. The Hopi Indians have also been shown to exceed DAM norms (Havighurst *et al.*, 1946) and Nepalese children show different patterns of response (Sundberg and Ballinger, 1968), so such variations are obviously not confined to these Malaysian children.

The observed differences in the DAM and DAW tests probably reflect variations in cultural background among the children of different races (Kuttner, 1970). Such variations are likely to affect a child's motivation and performance at school and perhaps in later life. It is currently fashionable to deny the existence of ethnic differences in intellectual skills. However, it would be more realistic to accept that different cultures may have particular strengths and weaknesses, and adjust educational methods and goals to enhance the strengths and compensate for the weaknesses.

We thank Miss Mei Li Li for scoring the drawings and Mrs Dianne Chandler for her assistance.

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Vomiting after pyloromyotomy for infantile hypertrophic pyloric stenosis

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SUMMARY An analysis of the factors which may predispose towards postoperative vomiting after pyloromyotomy for hypertrophic pyloric stenosis was carried out in 72 infants at this hospital. 26 (36%) infants experienced moderate to severe postoperative vomiting of sufficient intensity to cause the postoperative feeding regimen to be modified or interrupted. Only two parameters were found to be of statistical significance. These were the state of the oesophageal mucous membrane on endoscopical examination and the presence of haematemesis in the preoperative period. No evidence for a gastric mucosal lesion could be found. An advanced oesophageal mucosal lesion was found in 30% of patients, and this was the source of the haemorrhage in all 11 in whom haematemesis was noted preoperatively. The stay in hospital was prolonged (8 days) in those infants with troublesome vomiting postoperatively compared with those with lesser problems (3 days).

Vomiting after surgery for infantile hypertrophic pyloric stenosis is common, yet only vague statements about the problem can be found (Benson, 1969; Swenson, 1969; Cook and Rickham, 1978). In well documented analyses the incidence ranges from 65 to 90% (Table 1).

The precise cause of vomiting has been the subject of numerous reviews, and some authors have even attempted to identify those infants particularly at risk of developing troublesome postoperative vomiting. Haberer (1932) stated that most of the infants with postoperative vomiting 'showed blood in their vomitus preoperatively'. He presupposed a gastric mucosal lesion which required time to heal. Guiseffi (1948) noted that infants over 6 weeks tended to have a 'stormy' postoperative course. Terezis *et al.* (1959) identified a 3 to 8 times greater incidence of postoperative vomiting among infants having either preoperative alkalosis or a loss of >1·0 kg from their greatest attained preoperative weight. Unlike Guiseffi, they found that vomiting was more likely in infants aged 2 to 3 weeks than in ones who were older. Bell (1968) found no difference in the incidence of postoperative vomiting between infants with slight and those with gross metabolic disturbances. Schärli and Leditschke (1968) showed that gastric peristaltic activity had stopped 4–6 hours postoperatively, and that activity was depressed for an additional 16–24 hours. They concluded that early and frequent oral feeding during the first postoperative day was illogical and could lead to postoperative vomiting. Schärli *et al.* (1969) further showed that the incidence was unrelated to the duration of symptoms, to the preoperative serum bicarbonate level, or to special postoperative feeding routines. Benson (1971) suggested that postoperative vomiting could be made less likely by adequate preoperative fluid and electrolyte correction, by wide separation of all circular muscle fibres at surgery, and by avoiding oral fluids until 8 hours postoperatively.

Table 1 *Incidence of postoperative vomiting after pyloromyotomy in other series*

Author	*Year*	*No. of cases*	*Incidence of postoperative vomiting (%)*
Hayes and Goldenberg	1957	122	80
Pollock *et al.*	1957	1422	90
Prosser	1965	281	86
Bell	1968	305	69
Schärli *et al.*	1969	300	65

Incomplete pyloromyotomy as a cause of persistent vomiting is rare (Hayes and Goldenberg, 1957; Benson, 1971) and it is generally recommended that secondary pyloromyotomies should be postponed for 2 weeks after the first operation. Contrast radiography is of little help, as the radiological appearance of pyloric stenosis may persist post-

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operatively for several months even if the stenosis has been clinically relieved (Cremin *et al.*, 1973).

Excessive gastric mucus, secondary to diffuse gastritis, has been implicated by many authors (Rickham, 1969; Swenson, 1969; Dodge, 1975; Nixon, 1976; Cook and Rickham, 1978). They recommend gentle gastric washouts with warm normal saline preoperatively in order to evacuate the stomach of excess mucus.

This study was a prospective analysis of a consecutive series of 72 infants with pyloric stenosis at this hospital during a 3-year period 1975–78. The diagnosis was confirmed at operation in all cases.

The patients

The infants were fully assessed preoperatively, and any disturbance of fluid and electrolyte homeostasis or acid-base balance was corrected preoperatively. The stomach was evacuated of milk curds by gentle saline washouts in each. The pyloromyotomy was performed under general endotracheal anaesthesia and under the same anaesthetic an endoscopical examination of the oesophagus and stomach was carried out using the Olympus paediatric oesophagofiberscope, model EP type PA (maximum external diameter 7·2 mm). All the endoscopical examinations were performed by the same observer. A gastric mucosal punch biopsy was taken in 35 patients. No complications from the endoscopical examinations were encountered.

Classification of postoperative vomiting. Four grades of this symptom were recognised.

Grade I (n=10, 14% patients).
No vomiting at all postoperatively.

Grade II. Slight (n=36, 50% patients).
An odd vomit or occasional posset in the first 24–48 hours postoperatively.

Grade III. Moderate (n=14, 19% patients).
More frequent vomiting, sufficient to modify the postoperative feeding regimen.

Grade IV. Severe (n=12, 17% patients).
Excessive vomiting causing prolonged delay in establishing oral nutrition and often necessitating parenteral fluid administration.

The incidence for each grade of postoperative vomiting was assessed according to the following preoperative parameters. (1) Age of the infant on admission. (2) Sex. (3) Duration of symptoms. (4) Birthweight. (5) Degree of weight loss or failure to thrive. (6) Presence of haematemesis. (7) Feeding practice. (8) Size of the pyloric 'tumour'. (9) Appearance of the oesophageal mucosa on endoscopy. (10) Appearance of the gastric mucosa on endoscopy. (11) Presence of alkalosis. (12) Presence of dehydration.

For the purposes of statistical analysis the two grades with slight problems or none were combined (group 1) as were those with moderate and severe postoperative vomiting (group 2). This appeared to be a logical approach as the practical significance of the vomiting was determined by whether or not the postoperative feeding regimen had to be interrupted.

Statistical analyses used consisted of the χ^2 and Student's t tests if appropriate.

Results

Age on admission. The mean age on admission was 5·7 weeks, range 2 to 16. There was no statistically significant difference in the age on admission between the two groups (χ^2 0·9407, P>0·05). It is noteworthy that all 4 infants aged <3 weeks experienced pronounced postoperative feeding problems.

Sex. There were 55 boys and 17 girls in the series (ratio 3 : 1). This ratio was maintained in the various grades of postoperative vomiting.

Duration of symptoms. The mean duration of symptoms before admission was 15 days. There was no correlation between the duration of symptoms and the incidence of postoperative vomiting. (t 1·0309, P>0·05)

Birthweight. The mean birthweight for the 72 patients was 3200 g. There was no significant difference in birthweight between the two groups (t = 1·5480, P>0·05) and this applied equally to those infants weighing <2500 g at birth.

Degree of weight loss. The degree of failure to thrive was determined by measuring the difference between the expected and the actual weight on admission using the standard Tanner and Whitehouse growth chart. Seven infants displayed a positive growth pattern, 2 remained on their original centiles, while the remaining 63 infants failed to thrive. The average decrease in growth for the last group was assessed at −1·03 SDs from the mean. The degree to which infants in the two groups failed to thrive was not of statistical significance (t = 0·437, P>0·05).

Haematemesis. Eleven (15·3%) patients gave a positive history for blood in the vomitus preoperatively, either in the form of frank blood or 'coffee grounds'. Two had slight postoperative vomiting, while the remaining 9 experienced either moderate (7) or severe (2) vomiting. The difference was statistically significant (χ^2 9·5349, P<0·01).

Feeding practice. 24 infants were entirely breast fed while 40 were fed on a variety of proprietory milk formulae. Insufficient data were available in 8 patients. No difference could be determined in the incidence of postoperative vomiting according to feeding practice.

Size of the pyloric 'tumour'. The size of the pyloric tumour was subjectively estimated at operation to be small, moderate, or large (R. B. Zachary, 1975, personal communication). There was no correlation between the size of the 'tumour' and the frequency of postoperative vomiting (χ^2 2·9205, P>0·05).

State of the oesophageal mucous membrane. Endoscopically four types of oesophageal musoca were recognised: Grade 0—normal appearance (32 patients); I—slight erythema of the distal oesophagus only (18 patients); II—erythematous and friable mucosa (10 patients); III—presence of superficial ulceration of the mucous membrane (12 patients).

Analysis of the incidence of postoperative vomiting according to the above criteria is shown in Table 2. Although there was no statistical difference between the individual subgroups, infants with a normal or only slightly erythematous distal oesophagus experienced significantly less postoperative vomiting than those infants with a more advanced oesophageal mucosal lesion (χ^2 18·1983, P<0·001).

State of the gastric mucosa. No infant showed any evidence of a diffuse gastric mucosal lesion either on endoscopy or on histopathological examination of the mucosal biopsy (Batcup and Spitz, 1979). 19 (26%) infants displayed occasional punctate haemorrhages on endoscopy. There was no correlation between presence of punctate haemorrhages and the incidence of postoperative vomiting.

Alkalosis. 24 (33%) infants were biochemically alkalotic, as defined by a serum bicarbonate level preoperatively >28 μmol/l. No correlation could be found with the incidence of postoperative vomiting (χ^2 2·1747, P>0·05).

Table 2 *Degree of oesophagitis in relation to postoperative vomiting*

Oesophageal mucosal inflammation	*Degree of postoperative vomiting*			
	None	*Slight*	*Moderate*	*Severe*
Grade 0	7	20	1	4
I	1	11	4	2
II	1	3	3	3
III	1	2	6	3

Dehydration. There was no relation between the incidence and severity of clinical dehydration (28 patients), or azotaemia (11 patients) and postoperative vomiting (χ^2 0·7533, P>0·05).

Discussion

Of the various parameters analysed only two of statistical significance emerged—namely, the appearance of the oesophageal mucosa on endoscopical examination and the history of haematemesis preoperatively. It is noteworthy that of the 22 infants exhibiting a friable or ulcerated oesophageal mucous membrane on endoscopy, 11 (50%) gave a positive history for blood in the vomitus preoperatively. In view of the absence of evidence for gastritis endoscopically and on pathological examination, it can be concluded that the oesophageal, rather than the gastric mucosa, was the source of the haemorrhage in the infants in this series.

This finding is in direct contrast with the views of most authors on the subject (Benson and Lloyd, 1964; Swenson, 1969; Dodge, 1975; Nixon, 1976; Cook and Rickham, 1978). Forshall (1955) and Roviralta (1967) were the first to recognise the association between lower oesophageal sphincter incompetence and hypertrophic pyloric stenosis. Pellerin *et al.* (1974), in a retrospective study of 627 cases of hypertrophic pyloric stenosis with adequate radiological study of the hiatal region, demonstrated gastro-oesophageal reflux in only 13% of cases. Although it is generally recognised that oesophagitis commonly occurs secondarily to lower oesoghageal sphincter incompetence, the converse may equally apply. Lower oesophageal irritation may adversely affect the competence of the gastro-oesophageal mechanism (Eastwood *et al.*, 1975). Manometric studies of the oesophageal peristaltic activity were not undertaken in this series.

The finding of advanced oesophageal mucosal inflammation in 22 (30%) of the 72 infants, indicates that gastro-oesophageal reflux is more common than had been previously recognised. It has furthermore been shown to be a significant factor in the pathogenesis of postoperative vomiting in infants with hypertrophic pyloric stenosis. The effect of posture on the incidence of postoperative vomiting is currently being studied.

It is not my intention to advocate endoscopy on all infants with pyloric stenosis. The finding of oesophagitis in almost one-third of the infants was unexpected, but it has proved to be relevant with regard to the postoperative management of these infants. A positive history of haematemesis, which has been shown to be a consequence of the oesophagitis, should alert the clinician to the possibility of a complicated postoperative course.

Are the findings of this study relevant to clinical practice? The duration in hospital after pyloromyotomy is an important indicator. The postoperative hospital stay was prolonged in those infants with troublesome vomiting (mean 8·2 days) compared with the group with slight problems and in whom the feeding regimen was able to proceed without interruption (mean 3·6 days). The difference is statistically significant ($t = 6{\cdot}3263$, $P<0{\cdot}001$).

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Chronic pericardial constriction with effusion in childhood

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SUMMARY Five cases of children with nontuberculosis pericardial constriction with effusion are reported. The disease is not as rare as had been thought, and the aetiology in these cases was probably a previous virus infection. A previous diagnosis of hepatitis, nephrotic syndrome, or protein-losing enteropathy had been made and the correct diagnosis was delayed for months or even years. Pericardiectomy produced immediate relief from symptoms in 2 patients but in 2 others there was evidence of poor myocardial function postoperatively.

Constrictive pericarditis is rare, particularly in children. Watson (1968) estimated that: 'The disease represents not more than one in 10 000 cases of cardiac disease presenting in childhood in North America at present, but it may play a larger role in other countries particularly where tuberculosis is more prevalent'. The true incidence of the disease cannot accurately be given and it may be a good deal more common than Watson thought, as it is likely that some cases are asymptomatic and others are misdiagnosed. Five cases were seen in children during a 6-year period at the Bristol Royal Hospital, where about 300 new children with cardiac disease are seen annually, an incidence of 1 : 360 such children.

Case reports

Case 1.

History

A girl, born at 38 weeks' gestation birthweight 1820 g, was described as 'always a poor feeder from birth'. At 18 months mild lactose intolerance was diagnosed. She was referred here at 7 years with weight loss and increasing abdominal distension.

Examination

She was small and wasted (height 111 cm, weight 18·1 kg) with conspicuous abdominal distension due to ascites and hepatomegaly. The peripheral circulation was poor, the pulse small volume with obvious reduction in volume in inspiration, 'pulsus paradoxus'. The venous pressure was raised beyond the angle of the jaw. The cardiac impulse was faint and a very loud early diastolic sound was present.

Investigations

Chest *x*-ray showed an increased cardiothoracic ratio, the heart being visible as a separate shadow within the pericardium on one overpenetrated film. The presence of an effusion was confirmed by ultrasound examination. Mantoux test negative. Viral studies, including culture of ascitic fluid, negative.

Treatment

At operation (Mr R. H. R. Belsey), both parietal and visceral pericardium were considerably thickened in a uniform fashion and a sizeable effusion was found. The parietal pericardium was removed from the major part of both ventricles, as well as most of the visceral pericardium. Histology showed thickening and fibrosis, with moderate round cell infiltration.

Progress

Although initially she required antifailure treatment, 8 months later our patient was well and the heart was clinically and radiologically normal.

Case 2.

History

A girl was transferred to this hospital for investigation of hepatomegaly and ascites. She had been born by normal delivery at term. At 6 months she was noted to have bilateral interstitial keratitis. At age

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10 months she was admitted for investigation of abdominal swelling.

Examination
Obvious ascites, enlargement of the liver and spleen. Loud early diastolic sound.

Investigations
Chest *x*-ray showed considerable cardiomegaly and the heart shape was consistent with the presence of a pericardial effusion (Fig. 1). Tuberculin test consistently negative. Viral studies negative. Abdominal paracentesis on two occasions showed straw-coloured fluid. Transpleural liver biopsy was normal histologically. Her condition deteriorated after this procedure, and she developed pulsus paradoxus; cardiac tamponade was diagnosed. Pericardiocentesis was therefore performed, 150 ml greenish fluid being obtained, but the signs of tamponade recurred during the next 2 weeks.

Operation (Mr R. H. R. Belsey)
The heart was found to be surrounded by a densely adherent, grossly thickened visceral pericardium which was severely impeding cardiac filling. The parietal pericardium was thickened also, and was removed in its entirety, large portions of the visceral pericardium being dissected off the ventricles and removed also. Histologically the excised tissue showed dense fibrosis with scanty chronic inflammatory cells.

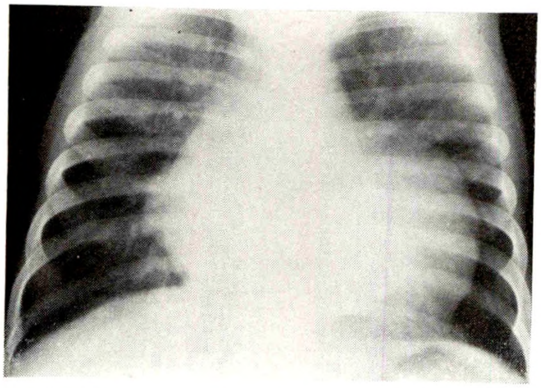

Fig. 1 *Case 2 x-ray. Cardiac shadow is enlarged but a faint medial opacity due to the heart itself is also shown.*

Progress
During the next 7 days large volumes of fluid drained from the left chest drain, but this gradually tailed off and thereafter her postoperative recovery was rapid and uneventful with prompt disappearance of all signs of impaired right heart filling. Five years later she remains perfectly well and the cardiovascular system appears normal.

Case 3.

History
A girl was noted at age 2 years to be breathless and cyanosed on exertion. Medical advice was not sought at that time and she presented at age 8 years with effort dyspnoea and occasional right-sided chest pain on exertion.

Examination
Slight central cyanosis. Small volume pulses. Jugular venous pressure greatly raised, with prominent A- and V-waves. No abnormalities were detected on auscultation. Liver palpable 3 cm below the right costal margin.

Investigations
Chest *x*-ray showed gross cardiomegaly with prominence of the superior vena cava and of the veins of the upper lobes of the lungs. Multiple opacities and septal lines were present at the bases, with a small right-sided pleural effusion. Tuberculin test negative. Antibodies to Q fever, psittacosis, *Mycoplasma*, mumps, and *Toxoplasma gondii* negative. Viral culture in HeLa and monkey kidney cells negative. Cardiac catheterisation (Table).

Operation
A pericardiectomy was performed (Mr G. Keen). The pericardium looked thickened and there was a moderate accumulation of pericardial fluid. Histologically the pericardium was moderately thickened but it was otherwise normal.

Table *Cardiac catheterisation*

Case	*Right atrium (mmHg)*		*Right ventricle (mmHg)*	*Pulmonary artery (mmHg)*		*Wedge (mmHg)*	*Left ventricle (mmHg)*	*A-V O_2 difference*	
	A-wave	*Mean*		*S/D*	*Mean*	*Mean*		*%*	*O_2 content*
3	36	28	100/12/25	100/65	80	26	100/12/25	54	9·6
4	9	8	35/ 6/ 8	33/12	18	12	—	—	—
5	30	25	42/15/25	40/30	32	26	—	39	6·3

Progress
Jugular venous pressure fell almost to normal and she was symptomatically greatly improved, but continued to show mild cardiomegaly and abnormal T-waves in the ECG. She died suddenly 2 years later, presumably from an arrhythmia.

Case 4.

History

A girl born by normal delivery at 38 weeks' gestation, birthweight 3200 g. She was admitted to hospital at age 2 months for investigation of convulsions. A chest *x*-ray showed a cardiothoracic ratio of 0·6, and an ultrasound cardiogram showed a moderate sized pericardial effusion and a small or normal sized heart.

Progress
Radiological signs of pericardial effusion remained for 2 years but then gradually subsided and our patient has since remained well.

Case 5.

History
A 2½-year-old girl was referred to this hospital with a one-year history of lethargy, oedema, and abdominal swelling. She was seen at another hospital and found to have albuminuria, and a tentative diagnosis of nephrotic syndrome was made; later this was changed to active hepatitis and then to protein-losing enteropathy.

Examination
Oedema of legs and face and moderate ascites. Liver 10 cm below the costal margin, jugular veins engorged with no obvious pulsation. A loud, early diastolic sound was audible all over the praecordium.

Investigations
Chest *x*-rays showed an enlarged cardiac shadow. ECG showed right and left atrial hypertrophy, small voltage QRS complexes, and flat T-waves (Fig. 2). Cardiac catheterisation (Table) showed findings

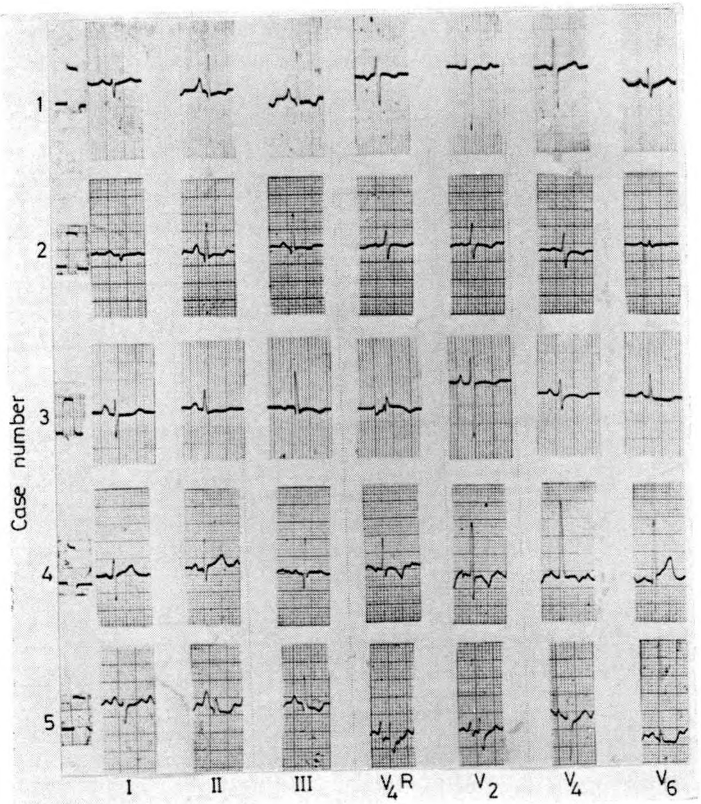

Fig. 2 *Preoperative electrocardiograms of the 5 patients.*

consistent with pericardial constriction, there being a pronounced 'dip and plateau' pattern in the right ventricular trace.

Operation (Mr R. H. R. Belsey)
The parietal pericardium was mildly thickened and distended by a large straw-coloured effusion. There was no adhesion of visceral and parietal pericardium. The pericardium was excised between the phrenic nerves. It was uniformly thickened with moderate numbers of chronic inflammatory cells.

Progress
Postoperatively the patient continued to drain moderate quantities of fluid for 7 days (1·6 litres) through the left pleural drain. After removal of the drain, fluid reaccumulated in the left chest and a further 2·8 litres were removed by repeated paracentesis, but eventually the effusion was controlled by frusemide 20 mg daily. During the next 6 weeks the dose was reduced and she remained well with a normal venous pressure and no abnormal signs. Four months after operation the venous pressure was again raised. The cardiac size on *x*-ray was within normal limits. Repeat cardiac catheterisation still showed equally raised right atrial and pulmonary wedge pressures. The chest was re-explored to exclude recurrent constriction but none was found. Six months later she still required a moderate dose of diuretic (10 mg frusemide daily) to keep her out of failure, and this has continued to do so to date.

Discussion

Aetiology. The 5 cases described have in common the presence of persistent pericardial effusion. This was associated with impaired heart filling in 4 and proved thickening of the pericardium in 3. The aetiology is obscure in all, although in 2 of the children there were associated features which support the suggestion of viral infection. Presumptive evidence for a virus aetiology to explain 'idiopathic' pericardial constriction was produced by Robertson and Arnold (1962) who found a cluster of about 5 such cases a year after an epidemic of virus pericarditis: 2 of their patients had had pericarditis during the epidemic (caused by Coxsackie B5 virus). In our Case 2 the coexistence of interstitial keratitis with negative serology for syphilis, and in Case 1 the low birthweight for gestational age and poor progress from birth, would be consistent with this possibility.

It was usually assumed, before the introduction of effective antituberculous chemotherapy, that tuberculosis accounted for most of the cases diagnosed as constrictive pericarditis. Simcha and Taylor (1971) stated: 'Tuberculosis plays a major role in the aetiology of constrictive pericarditis; strong evidence of this is found in this series'. This claim seems difficult to justify on the basis of their paper since in only one of 5 cases was a diagnosis of tuberculosis well established, and the evidence adduced in favour of this disease in 2 other cases was not convincing. Indeed, some doubt existed about the importance of tuberculosis as the main cause of constrictive pericarditis even before the introduction of streptomycin; of 37 cases (all children) reviewed by Rothstein (1934) tuberculosis was given as the diagnosis in only 9, with one doubtful, the remainder being attributed to rheumatism or 'unknown' in roughly equal proportions. Other authors (Mortensen and Warburg, 1948; Kuipers, 1955; Vining, 1955; Dalton *et al.*, 1956; Shea *et al.*, 1957; Caddell *et al.*, 1960) have presented small series of children, or included the occasional child in series of adults, but in these papers tuberculosis did not feature prominently as a proved cause. Even in countries where tuberculosis is common it probably only accounts for about half the number of cases (Das *et al.*, 1973).

Apart from tuberculosis, a variety of other disease processes have occasionally been found to cause constrictive pericarditis; these include histoplasmosis, Coxsackie pericarditis (particularly strains B3 and B5), traumatic haemopericardium, rheumatoid disease, hydatid disease, myxoedema, amyloidosis, sepsis (for example meningococcal and staphylococcal septicaemia), and malignant disease. Practically all accounts agree, however, that in any sizeable series the majority of cases occur in the absence of any identifiable primary disease, and the known causes, even collectively, constitute the minority (*British Medical Journal*, 1968; Keith *et al.*, 1968; Watson, 1968; Mullen *et al.*, 1969).

The role of acute rheumatism, if any, in the aetiology of constrictive pericarditis is not clear. Simcha and Taylor (1971) regarded it as hardly ever leading to constrictive pericarditis, while Rothstein (1934) attributed 13 of 37 cases to this cause.

Our 5 cases had moderately large, serous effusions, separating parietal and visceral pericardium. This is not generally a feature of tuberculous constrictive pericarditis, but is in keeping with the findings of Harrold (1968) in 3 adults with non-tuberculous pericardial constriction. Cayler *et al.* (1963) found moderately large pericardial effusions in their patients, but each one presented during the course of acute pericarditis.

Diagnosis. Although 2 of our patients presented with short histories and the diagnosis was suspected before referral, the other 3 were clearly undiagnosed for periods of several months or years. The failure to diagnose the presence of pericardial constriction was partly due to failure to notice or realise the significance of the raised venous pressure. If the venous pressure is so high that there is no longer obvious venous pulsation in the neck, the difficulties of assessment are well known. Another factor in the failure to make a diagnosis was the presence of secondary effects of the high venous pressure. Hepatic enlargement with abnormal liver function tests led to a diagnosis of active hepatitis and liver biopsy was performed (a procedure not without risk when the venous pressure is high). Similarly the effect of high venous pressure in the kidneys may cause a secondary nephrotic syndrome. Our Case 5 was similar in this respect to a 58-year-old patient reported by Pastor and Cahn (1960). Case 5 was initially diagnosed as having protein-losing enteropathy and this too has been reported as a complication of pericardial constriction (Plauth *et al.*, 1964).

The auscultatory signs in pericardial constriction are not obvious. Three of our patients had a loud, early diastolic sound, but this is often so early that it is mistaken for the second sound. The ECG is not specific and patients with only a small effusion, or none, may have a remarkably normal looking cardiac size and shape on chest *x*-rays. Diagnostic ultrasound (Feigenbaum *et al.*, 1967) is useful when there is a pericardial effusion.

Treatment. There were clear indications in 4 of our patients for surgical treatment. In one of them treatment was required fairly urgently for rapidly increasing signs of right heart failure and reduced cardiac output. In the other 3 there were obvious indications from the secondary effects of high venous pressure on the liver, kidneys, and gut. The surgeon's aim is to remove the thickened pericardium (visceral as well as parietal if necessary) from more than half the surface of the heart so that any further contraction of the remaining pericardium does not constrict the heart. In 2 of the operated patients the pericardial effusion separated parietal and visceral pericardium. In the other 2 a variable amount of dissection of pericardium from the heart itself was necessary. The exudative nature of the pericarditis is well shown by the 2 patients (Cases 2 and 5) who continued to drain fluid for several days or weeks after pericardiectomy. This was a surprising feature in view of the almost complete lack of signs of inflammation microscopically in the excised pericardium.

Myocardial involvement. Two of our patients (Cases 3 and 5) probably had chronic myocardial damage and Case 1 also showed temporary cardiac failure in the postoperative period. The possible reasons for myocardial involvement were reviewed by Levine (1973). Possible explanations are associated myocardial fibrosis (particularly if a viral aetiology is suspected), and the splinting effect of the constriction preventing the heart from dilating adequately.

We thank Dr J. A. Apley for permission to report Cases 1, 2, and 4 and Dr F. G. M. Ross for carrying out ultrasound cardiograms in Cases 1, 2, 4, and 5.

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Change of reference style

From January 1980, the *Archives* will change its style for citing references and will follow the number system. We are making this change in order to conform with the 'Vancouver style' of uniform requirements for manuscripts submitted to biomedical journals.

Previously the *Archives* has used the Harvard reference system. Its advantages and disadvantages compared with those of the number system have seemed evenly balanced, but the editors have been aware of the burden imposed on authors and their secretaries by the different styles which different journals require. Therefore, with the unanimous agreement of the editorial committee, we have decided to support a move whereby a large—and increasing—number of major medical journals will accept manuscripts presented in one agreed style.

The system numbers references consecutively in the order in which they are first mentioned in the text. References are identified in the text by arabic numerals. For further details see instructions to authors inside the front cover, and the references cited.[1,2]

From now onwards all manuscripts submitted should accord with the new style.

[1] International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979; **1**: 533–535.

[2] Lancet. The Vancouver style. Uniform requirements for manuscripts submitted to biomedical journals. *Lancet* 1979; **1**: 429–430.

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Short reports

Accuracy of pre- and postnatal assessment of gestational age

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SUMMARY The gestational age at delivery in a group of 20 neonates was estimated prenatally from measurements of the biparietal diameter made by ultrasound during pregnancy, and postnatally from the newborn infant's neurological and external physical criteria of maturity using the method of Dubowitz *et al.* (1970). These two assessments were compared with the gestational age at delivery calculated from the date of the last menstrual period (LMP) in mothers certain of their dates. Gestational age derived from the ultrasound data correlated well with that derived from the mother's LMP, and much better than did gestational age derived from the postnatal scoring system.

While the date of the last menstrual period (LMP) is accepted as the most accurate assessment of gestational age, provided that the mother is certain of her dates and has a regular cycle, such information is not always available and other methods have been sought. Antenatally, measurement of the biparietal diameter (BPD) of the fetus by ultrasound is increasingly applied as a routine part of antenatal care. Postnatally, physical and neurological criteria of maturity are used to assess the gestational age of the newborn infant, the most thorough method being that of Dubowitz *et al.* (1970). In this study these two methods were used to assess the gestational age at delivery in a group of 20 neonates, and compared with the gestational age calculated from the date of the LMP.

Methods

The neonates examined were singletons in the nurseries of the obstetric wards at Guy's Hospital. They were examined by the same person and scored according to the method of Dubowitz *et al.* (1970). If bilateral signs were different the more mature score was taken. Babies were examined within a few hours of birth. The results were not separated into male and female infants as it has been shown by Parkin *et al.* (1976) that there is no significant difference between their scores.

Information about the date of the LMP was collected from the antenatal notes by persons other than the examiner, and not seen by the examiner until all the neonates in the study had been seen and scored. Cases where the LMP was a withdrawal bleed from the pill rather than a true period were excluded from the study.

The estimated date of delivery was calculated from the LMP by adding on 280 days.

BPD measurements were obtained from the ultrasound department records, and the gestational age at the time of measurement read off from the cephalometry chart compiled by Campbell and Newman (1971), the gestational age at delivery being estimated by adding on the appropriate number of days. Only those infants who had had ultrasound measurements taken before 30 weeks' gestation were included, as Lunt and Chard (1974) showed that there is an increasing error in the measurement of BPD after 31 weeks. In most babies ultrasound measurements were made between 20 and 24 weeks, in one infant at

Table *Gestational age (weeks) at delivery as estimated from the Dubowitz score, ultrasound BPD measurement, and date of LMP*

Case	*Dubowitz score*	*Ultrasound BPD*	*LMP*
1	38	39·5	39·5
2	40	41·5	41·5
3	37	40	40
4	40·5	39·5	40
5	38·5	40	40
6	38	39	39
7	38·5	37·5	38
8	38	39·5	39
9	38·5	40	40
10	37·5	40·5	40
11	39	41·5	41
12	40	42	42·5
13	38·5	36	37
14	39·5	38·5	40
15	39	38·5	38
16	38·5	40·5	40
17	39·5	42	42·5
18	38	38·5	38
19	38·5	40·5	42
20	39	41	39·5

between 27 and 29 weeks, and in two between 16 and 20 weeks.

Results

The correlation coefficient for the ultrasound BPD and LMP estimations of gestational age was +0·8837, P<0·0005. The correlation coefficient for the Dubowitz scoring system and LMP estimations of gestational age was +0·4128, P<0·05 (Table).

Discussion

When the gestational age estimated by these two methods was compared with that estimated from the date of the LMP of mothers certain of their dates, the estimation using ultrasound data correlated much more closely with that derived from the LMP than did that using the method of Dubowitz *et al.* (1970). Thus when accurate LMP data are not available, the most reliable method of assessing the gestational age is by ultrasound BPD measurement early in pregnancy. The superiority of the ultrasound method is particularly relevant in the case of sick neonates; these should be handled as little as possible and will therefore be assessed on external criteria only, although less accurate than the method of Dubowitz *et al.* (1970) which comprises neurological as well as external physical criteria.

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Breast milk and breast feeding in very low birthweight infants

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SUMMARY The feeding of 17 babies weighing <1500 g was examined retrospectively. 12 babies started breast feeding at a mean weight of 1324 g and 10 of them were fully breast fed by a mean weight of 1600 g. Their weight gains were comparable with bottle-fed babies receiving expressed breast milk. Practical aspects of breast feeding were considered to be: a knowledgeable maternal and nursing attitude, close mother and baby contact, early expression of breast milk, and early suckling. The increased incidence of breast feeding by mothers of both low birthweight and term babies ensures regular supplies of fresh breast milk. Therefore, sterilisation or storage of breast milk here is unnecessary.

Interest in feeding low birthweight infants has been revived by numerous scientific analyses of the properties of breast milk (*British Medical Journal*, 1978). Many papers are preoccupied with differences between treated and raw breast milk, and with the storage of milk in banks (Ford *et al.*, 1977; Evans *et al.*, 1978; Williamson *et al.*, 1978). While tube feeding will inevitably be required in the management of very low birthweight babies, there is a danger that the ability of babies to suckle at the breast will be ignored and there are few studies on this aspect. Very low birthweight babies are usually the most difficult ones to feed. We therefore report on the management of the last 17 consecutive babies born in this unit weighing <1500 g, with particular reference to breast feeding.

Materials and methods

The babies weighed between 750 and 1500 g (mean 1272 ± 190 SD) and 13 were appropriate for gestational age. All babies were managed in a neonatal unit. Major complications were encountered by 2 babies who required ventilation, and 3 who required continuous positive airways pressure for respiratory distress syndrome or apnoea. 14 babies received IV fluids for a mean period of 3½ days. No other parenteral alimentation was given. The babies received 800 units vitamin D and 60 mg vitamin C daily after feeds were begun.

All babies were fed by a standard regimen of intermittent gastric gavage if their condition permitted. Breast or bottle feeding was started when sucking movements were noted. Gavage feeding was continued according to the success of breast feeding and satisfactory weight gain.

All low birthweight babies in this unit are fed expressed breast milk. Milk is manually expressed or allowed to ejaculate into sterile bowls and refrigerated. It is not boiled or frozen and is discarded after 24 hours. Milk was donated by mothers of babies in the neonatal unit and in the postnatal maternity ward. Mothers were asked about breast feeding within a few hours of birth and encouraged to express milk, particularly colostrum, to feed their babies. They were encouraged to assist with gavage feeding. Babies who were breast fed did not receive bottle feeds.

Weight gains of all babies were plotted on standard growth grids (Dancis *et al.*, 1948) and growth of head and length was recorded.

Results

12 babies started breast feeding at a mean weight of 1324 ± 99 g SD, and mean age of 11 days. The 10 babies who were successful were fully breast fed by a mean weight of 1600 ± 139 g, and a mean age of 27 days. All the breast milk for these babies was provided by their mothers from the 2nd or 3rd day postpartum. Of the 2 mothers who failed, one had waited for 30 days before starting breast feeds and was unable to keep lactating, the other fed for 5 weeks and gave up for 'convenience' just before discharge. Complete breast feeding usually coincided with stable temperature control and the babies were discharged at a mean weight of 1677 ± 104 g. Mean weekly weight gains for the 11 babies who were breast fed in the neonatal period are given in the Table. A transient slowing of weight gain after withdrawal of supplementary milk was common.

Table *Weekly weight gains (mean ± 1 SD) of breast- and bottle-fed babies*

	Weeks			
	1	*2*	*3*	*4*
Breast fed (g)	−82 ± 79	141 ± 40	148 ± 41	134 ± 73
Bottle fed (g)	−89 ± 59	133 ± 35	134 ± 81	159 ± 50

The amount of supplementary milk given to these babies was too variable to tabulate. The parents of these babies were white; one was unmarried.

The weight gains of the 6 babies given untreated expressed breast milk by bottle were comparable with those breast fed (Table). Of the mothers of these babies, 5 were of mixed blood (Maori, Indian, and European) and 5 were unmarried.

Discussion

This study shows that very low birthweight babies can be breast fed early. The mean weight and small standard deviation at which babies started breast feeding suggests that they are mature enough to suckle when they are about 1300 g. There were no complications attributed to early breast feeding. Successful breast feeding, particularly of very low birthweight babies, is attributed to many factors: unrestricted visiting of mother and family to the neonatal unit, an optimistic and knowledgeable attitude of the nursing staff to breast feeding, and babies to be breast fed being virtually never bottle fed. The problem of maintaining maternal milk secretion is paramount. Manual or hand pump expression of milk was used and we have no experience with mechanical breast pumps. On occasions, mothers breast fed other babies to stimulate milk secretion. Breast feeding a very low birthweight baby demands tremendous maternal commitment and co-operation, often for long periods. It is therefore essential to provide facilities for mothers to stay beside the neonatal unit without the usual hospital restrictions.

As would be expected, the main factor against breast feeding was maternal disinclination, strongly associated with sociological and racial factors.

Untreated expressed breast milk and breast feeding produced adequate weight gains in this small group of very low birthweight babies as judged from the weight grids used. Weight grids that are derived from cows' milk-fed low birthweight babies can, at best, only provide reference points. Optimum weight gains are unknown. The advantages of breast milk over cows' milk substitutes have been reviewed elsewhere (Addy, 1976; Jelliffe and Jelliffe, 1977). The use of untreated breast milk appears safe (Hack *et al.*, 1975) and probably preserves the antibacterial properties which are reduced by most methods of sterilisation (Ford *et al.*, 1977; Evans *et al.*, 1978).

The availability of milk has increased in recent years with the trend towards breast feeding. Therefore, in this region, storage of milk in banks is unnecessary. The present emphasis on milk storage and sterilisation is misplaced. The emphasis should be on educating and encouraging mothers to breast feed their own babies. A high rate of breast feeding in neonatal units and postnatal wards will ensure a ready supply of fresh expressed breast milk.

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Is it necessary to warm infants' feeds?

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SUMMARY The effect of temperature on gastric emptying after milk feeds was studied in 31 newborn infants. Test meals were a commercially prepared modified cows' milk (a) at body temperature and (b) at room temperature. Our results suggest that temperature has no effect on gastric emptying.

Before feeding a baby it is customary to warm the milk to approximately body temperature. This time-consuming procedure is presumably designed to mimic breast feeding as closely as possible. Even today when prepacked feeds are widely used, most mothers prefer to warm their babies' feeds, often using bottle-warmers which may be a fire hazard and a source of infection. Because food temperature has been shown to influence the rate of gastric emptying in adults (Ritschel and Erni, 1977) we decided to study the effect of feed temperature on gastric emptying in the newborn period.

Methods and infants

31 infants born in Aberdeen Maternity Hospital were studied. Their characteristics are shown in the Table. All the babies were being fed routinely via indwelling polyvinyl nasogastric tubes every 4 hours. The method of serial test meals used for adults (Hunt, 1951) had been modified for studying gastric emptying in the newborn (Husband and Husband, 1969). Initially the stomach was washed out with

Table *Gastric emptying in 31 newborn infants after test meals of 'warm' and 'cool' milk*

Case	*Gestational age (weeks)*	*Day of life started*	*Test meal (%) recovered from stomach after 30 min*	
			Warm	*Cold*
1	33	2	52·76	38·60
2	36	5	64·00	70·50
3	35	17	63·12	88·70
4	38	3	63·45	56·10
5	38·5	3	69·50	71·66
6	35	9	69·80	37·20
7	36	11	64·02	94·45
8	40	10	75·00	63·52
9	31	23	65·50	73·80
10	38	4	52·86	69·20
11	37	5	56·03	60·20
12	36	3	46·63	55·00
13	38	3	70·33	75·23
14	36	4	72·70	56·33
15	36	4	70·83	66·93
16	35	4	52·06	35·83
17	35	5	41·00	65·26
18	33	8	61·23	79·90
19	35	4	53·35	65·00
20	32	8	41·20	53·33
21	36	2	78·06	70·00
22	32·5	30	60·26	78·76
23	36	16	58·53	65·00
24	32	5	83·80	53·73
25	36	4	60·00	51·33
26	35·5	6	63·33	64·43
27	35	19	51·60	53·33
28	36·5	4	61·30	66·40
29	34	7	71·20	58·05
30	32	41	60·33	52·76
31	36	2	40·00	57·40
		Mean	61·72	62·10
		SEM	1·86	2·38

water until free of large curds. Test meals (20 ml/kg) were given 3 hours after the last feed and over a period of 3–4 minutes. After an interval of 30 minutes the gastric content was aspirated. The stomach was then washed out with 20 ml water to recover any remaining feed.

Test meals consisted of modified cows' milk formula (SMA Gold Cap) (a) at body temperature (37°C); (b) at room temperature (24°C). Phenol-red 0·24 mg/100 ml as a marker was added to these meals as it is not absorbed from the stomach and has no effect on gastric emptying (Hunt, 1956). Specimens obtained were kept frozen (−4°C) until analysed. Details of the calculations for estimating the gastric emptying rate are shown in the Appendix.

Both test feeds were given on the same day after two consecutive routine feeds. Each infant acted as his own control. Infants were nursed prone throughout the test.

Results

The results of the test meals are shown in the Table and Figure. A mean of 61·72% (± 1·86 SEM) of the meal was recovered after the 'warm' feed while the mean for the 'cold' milk was 62·10% (± 2·38 SEM). When these results were analysed by the Student's *t* test for pairs the difference was not significant ($t = 0{\cdot}14$; $P>0{\cdot}5$).

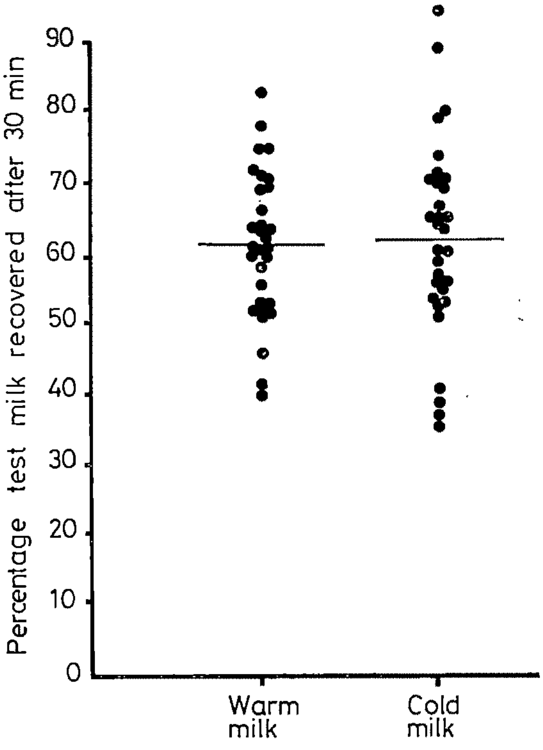

Figure *Percentage of test meal recovered 30 minutes after a milk formula given (a) at body temperature (37°C) (b) room temperature (24°C). Means for the solutions are shown,*

Discussion

Although it is traditional to warm a baby's milk before feeding there have been several trials with cold milk. Gibson (1958) gave 150 infants cold feeds from the refrigerator (4°C) and most accepted them without difficulty. Other studies investigated cold milk for feeding premature babies and no differences were observed in sleep patterns, vocalisations, motility, food or fluid intake, weight gain, or amount of regurgitation when compared with babies fed on warmed feeds (Holt *et al.*, 1962; Illingworth, 1972).

As these studies were based largely on clinical observations, it seemed reasonable to study the effect on gastric emptying as one physiological function which might have been altered by such a variation in feeding. Our results indicate that temperature changes within these relatively narrow limits have no effect on gastric emptying, unlike those of Ritschel and Erni (1977) and Erni and Ritschel (1977) who reported that an increase in temperature prolongs stomach emptying time. There are differences, however, between their methods and ours. The first study (Ritschel and Erni, 1977) was done on adult volunteers, and gastric emptying was studied using a Heidelberg capsule. Test meal consisted of water given at 4–6°C, 20–25°C, or 45°C. The second study (Erni and Ritschel, 1977) was done on rats. James (1957) supported the views of these authors, but did not present any further evidence.

Our failure to demonstrate any difference between feeds administered at room temperature and feeds given at body temperature might reflect the fact that the temperatures selected were not sufficiently different to have any effect. Gastric emptying time may be different after refrigerated milk, but in hospitals that use prepacked milk stored at room temperature there seems to be no advantage in warming the feeds to body temperature.

Appendix

Methods for estimating gastric emptying. The volume of the meal which is still in the stomach can be calculated from the total gastric content recovered, independent of added gastric secretions and saliva, by measuring the concentration of phenol-red (Hunt and Knox, 1962). A 10 ml aliquot of the liquid to be measured was pipetted into a test-tube. 1 ml of concentrated sulphuric acid was carefully

Example: Case 1 in the Table.

	Volume (ml)	*Optical density*
(a) Test meal	30	0·195
(b) Aspirate at 30 minutes	16	0·18
(c) Washout	21	0·01

Vol. of meal in (b) = (16 × 0·18 ÷ 0·195 = 14·76 ml
Vol. of meal in (c) = (21 × 0·01 ÷ 0·195 = 1·07 ml
Vol. of meal remaining in stomach at 30 min = 14·76 + 1·07 = 15·83 ml. % retention of meal at 30 min = 15·83/30 × 100 = 52·76%.

added drop by drop with shaking. It is important to add this acid slowly and to mix carefully to avoid charring the sample. When the whole ml of acid was added the tube was capped and thoroughly shaken and then allowed to stand for about 10 minutes. The acidified sample (pH approx. 1) was then filtered through filter paper no. 42. The clear filtrate was measured in a Vitatron colorimeter using a filter of 510 μm. The machine was put back to zero on water between each sample reading.

Approval for the study of gastric emptying in newborn infants was obtained from the Grampian Health Board, and University of Aberdeen Joint Ethical Committee.

We thank Dr G. Hems for statistical analysis of our results, and Miss Gordon of the Pharmacy Department, Royal Aberdeen Children's Hospital.

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Hepatitis A and Indian childhood cirrhosis

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SUMMARY Antibody to hepatitis A virus (anti-HAV) was found in 50% of patients with Indian childhood cirrhosis; this was not significantly different from the prevalence of anti-HAV in age- and sex-matched controls.

Indian childhood cirrhosis (ICC) is an important cause of mortality in young children in India (Indian Council of Medical Research Liver Diseases Sub-committee, 1955) but its aetiology has remained obscure (Nayak and Ramalingaswami, 1975). It has been suggested that the disease may be a sequel to infection with the virus of viral hepatitis (Achar *et al.*, 1960), but this has been questioned (Nayak *et al.*, 1972). Studies of hepatitis B surface antigen (HBsAG) in patients with ICC have not been conclusive (Chandra, 1970; Nayak *et al.*, 1975). In our experience, evidence of infection with hepatitis B virus can be found in 33% of patients with ICC. HBsAg was found by radioimmunoassay to be present in 18·8% of patients with ICC, and in another 14·2% patients, anti-HBsAg or HBc, or both, could be detected. Although this incidence is significantly higher than in control populations, infection with hepatitis B cannot account for all cases of ICC. Tests for the diagnosis of infection with hepatitis A virus are now available (Bradley *et al.*, 1977), and sera from patients with ICC were, therefore, tested for antibodies to hepatitis A virus (anti-HAV) by radioimmunoassay.

Materials and methods

The serum samples from patients with ICC and controls were collected during 1971–73 at the Children's Hospital, King George's Medical College, Lucknow. The clinical diagnosis and staging of ICC were made according to the criteria adopted from the report of the Indian Council of Medical Research Liver Diseases Sub-committee (1955). The sera were kept frozen at −20°C. Control studies have shown that anti-HAV is stable under these conditions.

Anti-HAV was measured by radioimmunoassay, as described by Bradley *et al.* (1977), in the hepatitis laboratories at the Center for Disease Control, Phoenix, Arizona. In this assay a ratio of equal to, or greater than, 2·1 between the test sample (P) and negative (N) sample (P/N ratio) was considered positive for anti-HAV.

Results and discussion

A total of 50% of the patients with ICC were positive for anti-HAV (Table 1). This number, however, was not significantly different from the prevalence of antibody in age-matched children who were admitted to the hospital for various illnesses other than those of the liver (Table 2). Although the prevalence of anti-HAV was higher in patients with stage I and stage II ICC than in those with stage III disease, the difference was not significant. There were also no great differences in the age distribution of patients in the three stages of the disease. The average P/N ratio for anti-HAV in patients with ICC was 14·6 ± 9·1 SD (range 3·1–31·3) and that in controls was 12·1 ± 8·3 (range 2·3–32·4).

In an endemic area the acquisition of antibody to an infectious agent is a function of age. This is clearly demonstrated by the age-related prevalence of anti-HAV in the patients with ICC as well as in their age-matched controls (Table 2). The prevalance of anti-HAV was no higher for ICC patients between birth and 2 years (42%) than in an age-matched control population (47%). These results do not support an aetiolcgical relationship of hepatitis A to ICC. However, the possibility that ICC may result from an abnormal response to infection with the virus of hepatitis A cannot be excluded. Determination of anti-HAV in serial serum specimens from patients with ICC may help to resolve this issue.

Table 2 *Antibody to hepatitis A virus in relation to age*

Age group (months)	*Patients with ICC*		*Children with diseases other than those of liver admitted to hospital**	
	Tested	*No. (%)*	*Tested*	*Positive No. (%)*
0–12	6	2 (33)	6	1 (17)
13–24	13	6 (46)	13	8 (62)
25–36	13	7 (53)	14	9 (64)
37–48	1	1	4	4 (100)

*Protein calorie malnutrition 5 (4 positive); nephrotic syndrome 5 (1 positive); Down's syndrome 4 (2 positive); bronchopneumonia 3 (3 positive); diarrhoea 3 (3 positive); normal children 3 (2 positive); poliomyelitis 2 (2 positive); miscellaneous 12 (5 positive), including one patient with kwashiorkor, one with intracranial space occupying lesion, one with eventration of left dome of diaphragm, one with splenomegaly of unknown cause, and one with short pyrexia of unknown origin.

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Table 1 *Antibody to hepatitis A virus in patients with Indian childhood cirrhosis*

Stage	*Age (months) mean ±1 SD*	*No. of boys*		*No. of girls*		*Total*	
		Tested	*Positive*	*Tested*	*Positive*	*Tested*	*Positive No. (%)*
I	26·1 ± 13·5	7	4	4	3	11	7 (64)
II	21·3 ± 10·3	6	2	4	4	10	6 (60)
III	23·0 ± 9·4	11	3	2	1	13	4 (31)
		24	9	10	8	34	17 (50)

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Should we follow up children with Henoch-Schönlein syndrome?

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SUMMARY We reviewed 31 children who had had Henoch-Schönlein syndrome without nephritis at least 5 years before. None was found to have progressive renal disease and these patients do not require the same long-term follow-up as those with clinical renal involvement.

Although there may be relapses of the abdominal pain, arthralgia, and rash of the Henoch-Schönlein syndrome (HSS) it is the degree of glomerular involvement which determines the long-term morbidity and mortality. About 70% of children have nephritis (haematuria or proteinuria) at presentation (Meadow, 1978) but evidence of renal involvement can be found by more elaborate investigations in most patients. In a few patients with HSS/nephritis the glomerular disease may progress to renal failure: we wondered if a similar deterioration could occur in those without clinical nephritis initially.

Patients, methods, and results

We reviewed the records of 79 patients who had presented with HSS before 1972 and found 52 without haematuria, proteinuria, or urinary casts on at least one occasion during the acute phase of the illness. 31 (19 boys and 12 girls) attended for re-examination: their course at presentation was no different from the nonattenders. The average age of onset of HSS was 5 years (range 7 months to 12 years 5 months), and at review was 12 years 7 months (8 years 4 months to 20 years 5 months) after an average interval of 7 years 11 months (4 years 5 months to 11 years 1 month). A medical history and blood pressure measurement were obtained, and the urine was examined microscopically for cells and casts and by dipsticks for blood and albumin.

Two patients, 8 and 9 years after HSS, had had periodic painless swelling of their knees which was thought to be of musculoskeletal origin rather than a persistent arthritis. The blood pressure was normal in all and urine normal in 28 of the 31 patients. Three boys who were otherwise normal had proteinuria which was transient in 2 and persistent in one (Table).

Discussion

The nephritis of HSS varies in its presentation from being asymptomatic to a rapidly progressive glomerulonephritis. Careful follow-up has shown that although in most patients the nephritis heals, in a few it does not. Of 88 patients followed up for more than 6½ years, 18 (20%) had progressive renal disease (Counahan *et al.*, 1977). Three of these patients who were normal at a 2-year follow-up now had more than 1 g proteinuria per day (1) or hypertension (2), while 6 patients with minor urinary abnormalities 2 years after HSS later showed heavy

Table *Details of 3 cases of Henoch-Schönlein syndrome with urine abnormalities at follow-up*

Case	*Age of onset (years)*	*Symptoms of acute disease*	*Age at review (years)*	*Blood pressure (mmHg)*	*Abnormality*
1	3·0	R, SS, AP, AR	10·5	80/40	+Proteinuria on 2 tests, 24-hour protein <0·1 g
2	5·0	R, AP, AR	15·0	105/60	+++Proteinuria on 1 test, trace on 1 test, 24-hour protein 0·3 g (7 mg/m^2 per hour). Further investigations refused
3	0·7	R, AR	9·9	100/60	Trace proteinuria on 1 test, negative on 2 further tests

R = rash, AP = abdominal pain, AR = arthritis, SS = scrotal swelling.

proteinuria (3), renal insufficiency (2), or hypertension (1). Focal proliferative glomerulonephritis with renal insufficiency (Meadow *et al.*, 1972), and temporary hypertension (Du Bois, 1969), have been reported in children with HSS and normal urinary sediment at presentation of the rash. Abnormal renal histology has been found in children with normal urine at onset of HSS (Greifer *et al.*, 1966) and it is likely that transient haematuria or proteinuria may be missed by once- or twice-daily urine tests. It therefore seemed possible that a few children thought not to have nephritis initially might deteriorate in the same way as the few with nephritis and show signs of renal disease at follow-up. If so, this might also explain the cause of some renal disease and hypertension in adults. The results of this study do not support this; they suggest that the prolonged follow-up of at least 5 years which is recommended for children with HSS/nephritis is unnecessary for those with normal urine at the onset of the rash.

We are grateful to Dr S. R. Meadow for reviewing the manuscript, Mrs V. Sessions and Mrs J. Gray for obtaining records, and Mrs J. Jordan for the typing.

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The following articles will appear in future issues of this journal:

Individualised continuous distending pressure applied within 6 hours of delivery in infants with respiratory distress syndrome. *A. K. Tanswell, R. A. Clubb, B. T. Smith, and R. W. Boston.*

Upper airways obstruction and apnoea in preterm babies. *A. D. Milner, A. W. Boon, R. A. Saunders, and I. E. Hopkin.*

Current status of zinc in health and disease states. *P. J. Aggett, and J. T. Harries.*

Sleep cycle studies in babies of undernourished mothers. *V. P. Bhatia, G. P. Katiyar, K. N. Agarwal, T. K. Das, and P. K. Dey.*

Effect of feeding on jugular venous blood flow in the normal newborn infant. *P. R. F. Dear.*

Treatment of a neonate with propionic acidaemia and severe hyperammonaemia by peritoneal dialysis. *M. F. Robert, D. J. Schultz, B. Wolf, W. D. Cochran, and A. L. Schwartz.*

Archives of Disease in Childhood, 1979, **54**, 905–906

Correspondence

Mourning by the family after a stillbirth or neonatal death

Sir,

In his article (*Archives*, 1979, **54**, 303), Dr Lewis suggested that mourning a stillborn child is facilitated by concentrating on the dead baby, and that an identity is created for the baby by the parents seeing and holding him, talking to the staff, and having a funeral and known burial place for him. Dr Lewis makes little of the more important and positive stages in the baby's development when he is alive and kicking *in utero*, very much existing and far from a nonperson, with both parents enjoying the pregnancy and the planning. It seems extraordinary to replace the memories of these stages, during which parents and the developing if unseen baby have a relationship, with those of a dead, cold, still, and possibly deformed baby. Even the baby of an early miscarriage may live long enough to be thought of as a person; more so is a baby who may have had as long as 20 weeks' visible and palpable activity. Occasionally the parents know before delivery that the baby has an abnormality incompatible with life; however this may not destroy the relationship although it must colour it. It is hard to see what the parents gain by substituting happy memories with ones which are at best negative and at worst shocking. While a funeral for a baby who has lived postnatally is important, it may do little for the parents of a stillborn child. We appreciate that Dr Lewis is looking for ways of making mourning easier for parents, but there is no room for dogmatism. A flexible approach is needed by all members of staff with the senior ones seeing that the conspiracy of silence, which he rightly condemns, is replaced by talking freely both in hospital and later at home.

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Dr Lewis comments:

Drs Jane Currie and Simon Currie reasonably wonder why I make little of parents' experiences of their babies *in utero*. In consultations with parents we do get them to relive these experiences, but they alone are not enough to facilitate mourning. Although a mother may have generally good feelings about her fetus, her ideas about its identity are necessarily poorly defined. This leaves room for much to go wrong. For instance, if parents have little sense of the personality of their stillborn baby, then the often quick replacement pregnancy, which itself tends to inhibit mourning, can be experienced as a continuation of the previous pregnancy. Then the newborn baby tends to be confused with the stillborn baby. This child may have a muddled sense of identity, suffer from a replacement child syndrome (Poznanski, 1972), or may be a victim of child abuse (Lewis, 1979).

As to contact with the dead baby being negative and shocking, fantasies reported by parents who have not seen their stillborn child are worse than the reality. Parents who have seen their stillborn child, including malformed babies. find relief in doing so and some treasure the experience.

Unfortunately, the psychological experience of stillbirth makes 'talking freely' rather difficult. GPs have been shown to have a strong reluctance to know, notice, or remember anything about a patient who has had a stillbirth (Bourne, 1968). Because a stillbirth is a void, a nonevent, it is difficult to think about, and it cannot occupy a potential thinking space in our minds. It is as if our very painful but vague thoughts about stillbirth occupy a wasteland, a black hole in the mind. Thus stillbirth is an empty drama that takes place at the interface of life and death: there is no catharsis. The experience of having made a baby tends to be annihilated by the experience of stillbirth. We encourage this annihilation by failing to acknowledge the stillbirth as having existed if we deny it a funeral.

The Curries, so keen to recognise the experience of the live fetus *in utero* as important, engage in doublethink when they feel a funeral for a stillbirth could 'do little' for the parents of the stillbirth. To the parents the baby does not cease to be important just because it hasn't breathed. Funerals are our society's way of marking the significance of death. A flexible approach sounds fine. Unfortunately, for the parents of a stillborn child, it often stands for unthinking inactivity, avoidance, and silence.

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Congenital absence of the sternum

Sir,

In the last few months we have seen 2 cases of congenital absence of the sternum in the newborn (as opposed to failure of fusion). There was no evidence of ectopia cordis nor was there any other congenital abnormality. A very detailed search for an aetiology was made but no cause could be found except for the fact that both the infants were born to mothers who came from south eastern Saudi Arabia where the diet is very deficient in vitamins, and both mothers had clinical evidence of panhypovitaminosis.

We think that this congenital abnormality in the infants may be due to chronic maternal riboflavine deficiency, as reported by Warkany and Nelson (1941) in experimental animals. Could I, through your columns, ask other paediatricians if they have come across this abnormality, and, if so, what was its aetiology?

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Acute inflammatory bowel disease in childhood: a new disease?

Sir,

We should like to report on the subsequent progress of the child described as Case 1 in the paper by Manuel *et al.* (*Archives*, 1978, **53**, 642).

This 6-year-old boy made a complete recovery after his initial illness and remained well for the next 2½ years. He then had an acute episode of diarrhoea and vomiting requiring no specific treatment, but the anorexia and diarrhoea persisted for 2 weeks. Six weeks later he became constipated. This did not respond to treatment with laxatives nor did it respond to repeated enemata over the next 4 months. He also began to have abdominal pains, which were thought to be due to his severe constipation, and he developed painful anal fissures.

Physical examination at this time showed no abnormality apart from a rather scarred anus with two fissures, but colonoscopy revealed scattered aphthoid ulcers throughout the colon characteristic of Crohn's disease, and an ulcerated terminal ileum.

The typical noncaseating granulomata, found in Crohn's disease, were present in the biopsies from the terminal ileum, confirming this diagnosis. He was started on sulphasalazine. He responded satisfactorily, with return of his stools to normal, disappearance of his abdominal pain, and healing of the anal fissures. He has since remained well.

It is interesting to speculate what relationship the initial illness reported in the *Archives* may have had to the subsequent one. Was this an acute presentation of Crohn's disease? This was considered at that time as it is rare to have a diarrhoeal illness of such severity in a child 6 years of age in this country. However at that time none of the usual diagnostic features of Crohn's disease was present—namely the barium follow-through examination did not suggest Crohn's disease, and the abnormality on small intestinal biospy was severe but nonspecific, with an acute inflammatory cell reaction. Was the initial illness in fact a severe attack of acute gastroenteritis which, in some way, has precipitated the development of Crohn's disease in a susceptible individual? The answer to these questions is uncertain, and it remains quite possible that the two illnesses were unrelated. Nevertheless this case illustrates that although spontaneous resolutions can occur in acute inflammatory bowel disease for which no cause has been found, the eventual diagnosis of chronic inflammatory bowel disease is not thereby excluded, and long-term follow-up is necessary in children in whom this diagnosis is made.

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Archives of Disease in Childhood, 1979, **54**, 907–908

Book reviews

Pediatric Surgery. Third edition, in two volumes. Edited by M. M. Ravitch, K. J. Welch, C. D. Benson, E. Aberdeen, and J. G. Randolph. (Pp. 760 (volume 1), 862 (volume 2); illustrated + tables. £135.00 hardback (2 volumes cased). YB Medical Publishers: Chicago. 1979.

This book, the most comprehensive on the subject, is widely respected throughout the world and this 3rd edition maintains this high standard. Two of the 5 editors for this edition are new, as are two-thirds of the 152 authors. The result is that the current edition has been extensively revised and changed. 85% of the authors are from the USA and, with those from Canada, this gives the book some North American bias. As paediatric surgical problems are similar throughout the world this does not detract from the high international standing of the book. The content is wide ranging. It starts with a general section in which genetics, naesthesia, intensive care, and general spects of management are considered. Next trauma in a broad sense is discussed, rom nonaccidental injury with all the sual injuries to less common ones—such s snake and spider bites. In the remaining wo sections the head and neck, and horax and cardiovascular system are discussed. Vol. 2 is divided into sections hat deal with the abdomen, the genito-urinary system, the integument and musculoskeletal system and, finally, the nervous system.

One addition which seems to contribute little to the book is that of some colour lates, but apart from these, the illustrations and presentation are of a high tandard. In a work of this size it is nevitable that there will be an occasional detail which escapes the editors—such as he omission of duplications in the index despite a chapter on duplications) or the mission of any discussion on hypertension in neuroblastoma (despite two earlier references to this). The only facet which does not seem to have adequate cognition is the use of diagnostic ltrasound, despite the considerable dvances achieved with this technique. However the editors must be congratulated on the very high standard they and the authors have set and maintained.

No unit undertaking paediatric surgery should do without this book, although its cost may make some units think twice before purchasing. The investment will be worth while.

D. G. YOUNG

Pediatric Trauma. Edited by R. J. Touloukian. (Pp. 646; illustrated + tables. £24.95 hardback.) Wiley: Chichester. 1978.

This book with its 22 collaborators, all widely known in paediatric surgery, aims to describe in detail the special factors in the care of the injured child from the time he or she is first picked up at the site of the accident. These are: transport, resuscitation, diagnosis, anaesthesia, operation, postoperative management, and rehabilitation.

Accidents are so common in childhood that a good book of this type is always worth having. In the first part there is detailed description of the psychological effects of injury, of anaesthesia and resuscitation, birth injuries and battering, while in the second part, injuries of the organ systems are dealt with in detail and the diagnosis of management in each system is well described. A surgeon might be forgiven for questioning whether the properly trained paediatrician should assume the role of team captain, as is suggested in the preface to this book, and while some minor injuries may be treated by a physician without the help of a surgeon, many of the major injuries described in this book depend on good surgical management and perhaps it is not too old-fashioned to hope that the surgeon should be called in and that he will even be among the first to see the patient.

There is an excellent chapter on evaluation and initial management which could be read with profit by anyone who deals with injured children. This is an excellent book and, unlike some which have purported to deal with injuries in childhood, this one really does. It also sticks to the problems of the child rather than slipping in little bits of adult surgery here and there. There are many good line drawings and indeed some of these are much better than the photographs. There are good and extensive lists of references at the end of each chapter. This book can be recommended as a good guide for those who need help in the treatment of the injured child. It should be in any hospital which treats children.

A. W. WILKINSON

Spinal Muscular Atrophy: Infantile and Juvenile Type. Edited by Irena Hausmanowa-Petrusewicz. (Pp. 180; illustrated + tables. $9 North America; $18 foreign, hardback.) National Center for Scientific, Technical, and Economic Information: Warsaw. 1978. (Available from US Department of Commerce, National Technical Information Service, Springfield, Virginia 22161, USA).

This valuable monograph is based on the rich experience of the Department of Neurology, Warsaw School of Medicine.

It is divided into 14 chapters that cover history, clinical features, classification, morphology, electrophysiology, radiology, psychology, biochemistry, immunology, differential diagnosis, prognosis, genetics, and treatment. The author's experience is compared with that of other workers. There are 521 references and the many pathological illustrations show clearly the changes detailed in their captions. The translation is excellent.

The Warsaw classification of these disorders differs from that more widely used, but the relationship between their type Ia cases (classical Werdnig-Hoffmann disease), type Ib (protracted cases of Werdnig-Hoffmann), type II (intermediate between these two extremes), and type III (Kugelberg-Welander disease) is clearly stated. The total of 310 cases is made up of 79, 77, 59, and 95 respectively in these four categories.

The muscle biopsies are compared with control biopsies from young children (from another source). Muscle cells from affected children show a morphological resemblance to fetal muscle, and this, with a fetal-type muscle protein pattern and the interesting electrophysiological finding in Werdnig-Hoffmann disease of initially slow peripheral nerve conduction velocity, which later becomes normal, suggests that spinal muscular atrophy may be due to persistence of fetal features. This hypothesis suggests that the difference between the various clinical types depends on the number of fibres affected during fetal life, and the stage of fetal development when the presumed insult responsible occurs.

The section on prognosis is very brief and I was disappointed not to find more information based on the large number of cases.

The chapter on treatment is necessari short, but it is interesting to read of therapeutic approach with vigoro exercise in the group III patients.

This is an important book for all wl are interested in these disorders.

E. M. BRE

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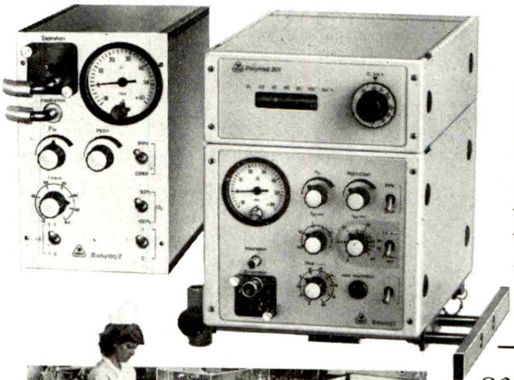

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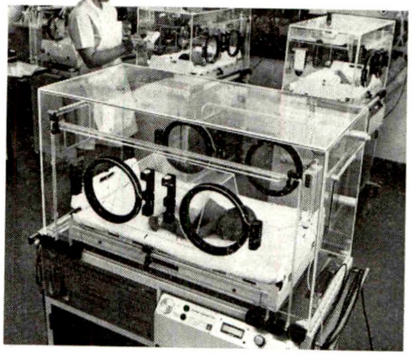

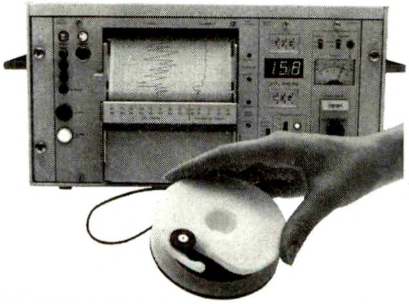

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Archives of Disease in Childhood, 1979, **54**, 909–917

Review article

Current status of zinc in health and disease states

P. J. AGGETT AND J. T. HARRIES

Institute of Child Health, London

Even though brass, a zinc-copper alloy, had been known for centuries, metallic zinc was not isolated in Europe until 1509. The metal was then named zinken because of its superficial similarity to tin (German–zinn) (Wootton, 1910).

Zinc (atomic number 30; atomic weight 65·37) has a completed d subshell with 2 s electrons and the divalent cation is the only naturally occurring oxidation state. This relative stability, its ability to co-ordinate 4 or occasionally 6 ligands, and its capacity to act as a Lewis acid are probably fundamental to zinc's biological role. The biological importance of zinc was first discovered when Raulin (1869) demonstrated that it was necessary for the growth of *Aspergillus niger*. Subsequently, the ubiquitous distribution of zinc in nature was appreciated and the essentiality of zinc for higher plants (Mazé, 1914) and animals (Todd *et al.*, 1934) was established.

In man the medicinal use of calamine (zinc carbonate) is first recorded in *Papyrus Ebers* of 1550 BC (Ebers, 1937) but it was not until 1939 that it was suggested that zinc deficiency might contribute to the clinical manifestations of human vitamin deficiency syndromes such as beriberi (Eggleton, 1939). The first human zinc deficiency syndrome was identified in the early 1960s in malnourished adolescent boys in Iran and Egypt (Halsted *et al.*, 1972). A more profound deficiency state became apparent when Moyanhan and Barnes (1973) showed that treatment with zinc induced a complete and rapid clinical remission in a patient with acrodermatitis enteropathica.

Dietary sources and requirements

Good dietary sources of zinc (Underwood, 1977) are meat (20–60 μg (0·3–0·9 μmol)/g wet weight, and fish (15 μg (0·2 μmol)/g wet weight). Although cereals and vegetables have similar zinc contents (15–60 μg/g wet weight) to meats, the bioavailability of zinc from plant sources is reduced by their high phytate (inositol hexaphosphate) content which complexes the metal and prevents its absorption (Becker and Hoekstra, 1971). Diets containing phytate and zinc with a molar ratio in excess of 25:1 induce growth retardation in young rats (Davies and Oppin, 1979). Momcilovic *et al.* (1976) showed that the availability of zinc from a soya-based infant feed may be reduced by 20%. Complexation also occurs with fibre, hemicellulose, and clay; cellulose bulking agents reduce the absorption of the radioisotope ^{65}Zn (Becker and Hoekstra, 1971). Both calcium and phosphate reduce the utilisation of dietary zinc. Chelating agents such as EDTA, and animal protein may improve zinc availability from plant materials (Becker and Hoekstra, 1971), and its content in and availability from foodstuffs may be altered during food preparation (Halsted *et al.*, 1974).

The zinc content of cows' and human milk is variable (Picciano and Guthrie, 1976) and comparisons are unreliable. Human milk contains a low molecular weight zinc-binding ligand which probably facilitates absorption (see later); such a ligand is not present in cows' milk and zinc from this source to the human infant may be reduced (Eckhert *et al.*, 1977). A recent study on 6-month-old infants showed higher plasma zinc levels in those which were breast fed than in infants fed cows' milk-based formulae (Hambidge *et al.*, 1979). A longitudinal study has demonstrated that human breast milk zinc concentrations decrease with the duration of lactation (Vuori and Kuitunen, 1979). These are facts that need to be considered when evaluating the zinc nutritional value of infant feeds and of mature breast milk, especially when it is given to preterm infants in whom absorptive mechanisms may be immature (see later).

An adult consumes 10–15 mg (Underwood, 1977) of dietary zinc a day and the following age- and sex-related daily dietary allowances have been recommended by the National Research Council

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P. J. AGGETT, co-ordinator
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J. T. HARRIES, reader in paediatrics

Food and Nutrition Board (1974): 0–6 months, 3 mg (46 μmol); 6–12 months, 5 mg (76 μmol); 1–10 years, 10 mg (152 μmol); adolescent children, adult men, and nonpregnant women, 15 mg (230 μmol); pregnant women, 20 mg (305 μmol), and lactating mothers 25 mg (382 μmol). A WHO Expert Committee (World Health Organisation, 1973) prepared recommendations based on the bioavailability of dietary zinc but all such recommendations can only serve as tentative guidelines. In healthy children in the UK, Alexander *et al.* (1974) demonstrated an average daily intake of 0·3 mg (4·6 μmol)/kg; about 20% of which was absorbed.

Absorption

Zinc absorption occurs throughout the small intestine but most rapidly in the duodenum and proximal jejunum (Methfessel and Spencer, 1973), and is probably a carrier-mediated process (Davies, 1974). *In vitro* uptake studies in human small intestinal mucosa suggest that it is also an active energy-dependent process (Atherton *et al.*, 1979) and isopycnic ultracentrifugation studies (unpublished) on isolated enterocytes from this material indicate that the absorbed zinc is almost totally distributed in the cytosol fraction. ^{65}Zn can be detected in plasma 15 minutes after ingestion and reaches a peak 4 hours later (Spencer *et al.*, 1966); patients with an ileojejunal bypass appear to have reduced zinc absorption (Andersson *et al.*, 1976).

Low molecular weight (8000–10 000) zinc-binding ligands (ZBL) have been reported in the small intestine and pancreas of rats, in the pancreatic secretions of dogs (Evans, 1976a), and in rat and human milk (Hurley *et al.*, 1978). Although the precise functions of these ZBL have not been defined, they almost certainly facilitate zinc absorption from the intestinal lumen. The mucosal ZBL is absent in the newborn rat which is dependent on the maternal milk ZBL for optimum zinc absorption. This dependence is lost after 18 days, by which time the mucosal ZBL has developed and the exogenous ZBL no longer enhances zinc absorption (Duncan and Hurley, 1978). A similar process may operate in the human since some term and low birthweight preterm infants have an impaired capacity to absorb zinc (Cavell and Widdowson, 1964; Dauncey *et al.*, 1977) and the human breast milk ZBL content is highest in colostrum and diminishes thereafter (Hurley *et al.*, 1978).

A low molecular weight cytoplasmic zinc-metalloprotein designated zinc-metallothionein (Zn-MTN) because of its high cysteine content, has been identified in the liver and small intestinal mucosa (Cherian and Goyer, 1978), and its synthesis can be induced by parenteral or oral administration of zinc (Richards and Cousins, 1975). Its precise function is undefined but it may participate in the homeostatic regulation of zinc metabolism and absorption, and provide a source of zinc at times of deprivation. The relationship between ZBL and intestinal Zn-MTN has not been clarified. Zn-MTN may regulate zinc absorption by sequestering zinc within the enterocyte. This possibility is supported by the observation that there is an inverse relationship between intestinal zinc uptake and intestinal MTN content (Richards and Cousins, 1976). It has been suggested that zinc is taken up from the enterocyte basolateral membrane by transferrin and conveyed to the liver via the portal vein (Evans, 1976a, b). The mechanism of cellular uptake of zinc and its incorporation into metalloproteins has not been elucidated but the latter probably occurs after the synthesis of the apoprotein.

Excretion

The main excretory route for zinc is in the faeces (Underwood, 1977). Biliary losses are small but pancreatic secretion may contribute 25% of endogenous zinc loss (Stake *et al.*, 1974). The relative contributions to the remaining faecal loss by desquamation of surface epithelial cells or intestinal secretion has not been defined.

Renal conservation of zinc results in a daily urinary loss <600 μg (<9·2 μmol) (Underwood, 1977). The zinc concentration in neonatal urine may be 5 times that of adults (Cavell and Widdowson, 1964).

Sweat zinc loss is negligible in preadolescent children studied in temperate areas (Harrison *et al.*, 1975), but in tropical climates it may be significant. Secretion by this route is reduced with acclimatisation and in zinc deficiency states (Prasad *et al.*, 1963).

Body zinc distribution and mobilisation

A 70-kg man contains 1·4–2·3 g (21–35 mmol) of zinc (Widdowson *et al.*, 1951) and a term neonate has about 60 mg (0·9 mmol) (Widdowson and Spray, 1951). In the adult, this amount is about 40% of the total body content of iron and 10–20 times that of copper; there is relatively less zinc in the neonate and the corresponding ratios are 20% and 5 times respectively. Next to potassium, calcium, and magnesium, zinc is the most abundant intracellular metal and is located principally in the supernatant, microsomal, and nuclear fractions (Thiers and Vallee, 1957). Highest tissue concentrations (>500 μg (>7·7 μmol)/g dry weight) are found in the uveal tract, and postpubertal prostate gland and seminal fluid. Hair, nails, skin, and bones have a zinc content of 90–250 μg (1·4–3·8 μmol)/g, and the pancreas, liver, kidney, and muscle contain 140–230 μg (2·1–3·5 μmol)/g (Halsted *et al.*, 1974). Muscles in newborn animals have a similar zinc content but active muscle groups soon develop higher concentrations than less active groups (Cassens *et al.*, 1967).

Studies using ^{65}Zn show poor exchange of zinc deposited in bone, skin, and muscle and poor zinc mobilisation from these sources in rats at times of increased requirements, such as pregnancy (Hurley and Swennerton, 1971), suggest that these tissues which collectively contain 70–80% of the total body content of zinc do not provide an effective storage depot. In the young growing animal, however, release of bone zinc during the remodelling process may provide a reserve source (Brown *et al.*, 1978). The fetal zinc content increases in proportion to body weight and there is little evidence of intrauterine storage of the element; however the possibility that hepatic zinc in the neonate may provide an additional store remains to be elucidated.

Erythrocyte zinc (10–14 μg/g) (Halsted *et al.*, 1974) is predominantly located in the enzyme carbonic anhydrase and comprises 75–88% of the whole blood zinc content, the remainder being principally in the leucocytes (3%) and plasma (12–20%) (Vallee and Gibson, 1948); individual leucocytes contain about 25 times as much zinc as erythrocytes. Most of the plasma zinc is bound to albumin (50%) and an α_2-macroglobulin (30–40%), a small amount is associated with a β-globulin (transferrin) and with free amino-acids (2–8%) (Prasad and Oberleas, 1970).

Analytical values of plasma zinc vary slightly with the technique used for their assay but most laboratories providing such a service have determined their own normal range. The paediatric range established at The Hospital for Sick Children, London (Aggett *et al.*, in preparation) is 11–24 μmol/l (72–157 μg/100 ml).

Plasma zinc levels fall within hours of stress—such as surgery, trauma, or inflammation—and remain low with chronic stress. This is caused by a protein, leucocyte endogenous mediator (LEM), which is released from activated phagocytes and which enhances hepatic uptake of zinc and iron as well as synthesis of acute phase proteins including caeruloplasmin (Beisel *et al.*, 1976). Zinc is redistributed among its plasma ligands, and increased binding to low molecular weight ligands such as amino-acids may underlie the zincuria which can accompany stress. It is unclear at present whether LEM is a number of similar proteins or a single multifunctional entity. Plasma zinc levels are also frequently depressed in patients with neoplasia.

Assessment of zinc status

There is no reliable means currently available for determining the body zinc status in routine clinical practice. Plasma zinc levels are subject to acute variations and a single low value should be interpreted cautiously in conjunction with other factors, such as the patient's clinical condition. Serum levels are 16% higher than plasma levels partly as a result of the release of zinc from platelets and unavoidable haemolysis (Foley *et al.*, 1968). Hair zinc levels correlate poorly with plasma levels but provide historical information which is of value in epidemiological studies. Low hair zinc levels in one study were associated with zinc-responsive symptoms (Hambidge *et al.*, 1972) and probably represented previous zinc nutritional status. The interesting report of Heinersdorff and Taylor (page 958) showing a lower hair zinc content in boys aged 10–11 compared with similarly aged girls may reflect other, possibly physiological, influences which merit further investigation. Erythrocyte or leucocyte zinc determinations may prove to be more reliable then plasma levels, but the fact that the erythrocyte zinc content rises progressively during the first 12 years of life (Berfenstam, 1952) limits its application in children. Determination of urinary zinc is also unreliable, but it has been suggested that the urinary sulphate content could be of some value (Hsu and Anthony, 1971). In some studies salivary zinc has been measured (Henkin *et al.*, 1975a). Tissue analysis, ^{65}Zn turnover, and balance studies are essentially research tools. It should be stressed that all specimens for zinc determination must be collected with great care and stored in zinc-free containers to avoid haemolysis and contamination. Reduced activity of zinc-dependent enzymes, such as alkaline phosphatase, often accompanies a reduction in plasma zinc in deficiency states, and may provide a valuable clue particularly when facilities for determining zinc are not readily available. At present, the best criterion of zinc deficiency is an unequivocal clinical response to zinc administration.

Biological functions

Enzyme activities. Zinc is essential for the activity of at least 90 enzymes which participate in all the major metabolic pathways. Over 40 metalloenzymes exist in which zinc is bound tightly to the apoenzyme in specific stoichiometric ratios and in which it serves one or more structural, regulatory, or catalytic functions (Riordan and Vallee, 1976). Mammalian metalloenzymes include carbonic anhydrase, carboxypeptidases, aminopeptidases, alkaline phosphatase, alcohol, retinol, malate, lactate, glutamate, and glyceraldehyde-3-phosphate dehydrogenases. Some metalloenzymes require additional metals for activity, cytosolic superoxide dismutase, for example, has a requirement for copper as well as for zinc.

Other metalloenzymes have only been identified in lower species and the particular metal dependence of an enzyme varies between species. Both DNA and RNA polymerases are zinc metalloenzymes in *Escherichia coli*; it has not been established that these are metalloenzymes in mammals but studies on animals indicate that thymidine kinase activity and nucleic acid synthesis are zinc-dependent in mammals. In some oncogenic viruses the reverse transcriptase (that is, RNA-dependent DNA polymerase) is a zinc metalloenzyme (Vallee, 1977). There is evidence that zinc is important for optimal activity of aspartate transcarbamylase, δaminolaevulinic acid dehydratase activities (Riordan and Vallee, 1976), ornithine transcarbamylase (Rabbani and Prasad, 1978), and in fatty acid metabolism (Hambidge *et al.*, 1978).

Zinc-deficient animals have impaired collagen synthesis and poor wound healing. This may reflect a generalised defect in protein and nucleic acid synthesis; however some evidence suggests that zinc deficiency alters the quantity and type of collagen cross links (Fernandez-Madrid *et al.*, 1976).

Cell function. Zinc is essential for all phases of the cell cycle, but, as yet, there is little evidence to relate this directly to its effects on nucleic acid and protein synthesis. Deficiency is associated with RNA disaggregation and increased ribonuclease activity (Prasad and Oberleas, 1973), and the ability of zinc to inhibit adenylate cyclase and phosphodiesterase may indicate a role in cell function and genetic expression by regulating the relative intracellular concentrations of cyclic-AMP and cyclic-GMP (McMahon, 1974). Cell replication rates in the oesophagus and pancreas of zinc-deficient rats are increased (Fell *et al.*, 1973), suggesting that a loss of genetic regulation precedes an effect on nucleic acid and protein synthesis. In human lymphocytes zinc acts as a mitogen, but here again the mechanism is unclear but appears to be mediated by monocytes (Rühl and Kirchner, 1978). Zinc stabilises plasma and subcellular membranes (Chvapil, 1976) as well as nucleic acids and microtubules (Nickolson and Veldstra, 1972); it stabilises lysosomes and high concentrations *in vitro* inhibit leucocyte mobility and phagocytosis while enhanced macrophage migration has been described in zinc-deficient guinea-pigs (Chvapil, 1976); membrane lipid peroxidation is increased in zinc deficiency states, and it has been proposed that zinc protects membranes from free radical oxidation (*Lancet*, 1978).

Endocrine function. Insulin is stored in the β-cells of the pancreas as a hexamer with 2 atoms of zinc (Adams *et al.*, 1969), and zinc appears to influence insulin binding and degradation at the hepatocyte plasma membrane (Arquilla *et al.*, 1978). In some studies impaired glucose tolerance and insulin response have been associated with zinc deficiency, but this has not been a consistent feature (Kirchgessner *et al.*, 1976).

Prostatic androgen metabolism is modified by the intracellular concentration of zinc, and both high and low tissue concentrations inhibit the transformation of testosterone to dihydrotestosterone (DHT) (Habib, 1978). Hartoma *et al.* (1977) demonstrated improved sperm counts and testosterone levels in hypozincaemic oligospermic males as a result of zinc administration; this treatment has also reversed uraemic impotence and increased DHT levels in patients with renal dialysis (Antoniou *et al.*, 1977).

Taste. It has been suggested that zinc may play a physiological role in taste (Henkin *et al.*, 1975a, b) and in this context is it of interest that 2 similar zinc metallo-proteins, gustin and nerve growth factor, have been isolated from human and murine saliva respectively and appear to combine with their respective taste buds and to be essential for their normal morphology and optimum function (Henkin, 1978).

Zinc deficiency states

Zinc deficiency can result from an inadequate dietary intake, malabsorption, increased body losses, intravenous feeding, or a combination of

Table 1 *Causes of zinc deficiency*

- Inadequate dietary intake
  - Protein-calorie deficiency
  - Vegetarianism
  - Patients on protein-restricted diets
  - Synthetic diets
- Malabsorption
  - Acrodermatitis enteropathica
  - Coeliac disease and other enteropathies
  - Pancreatic insufficiency
  - Chronic inflammatory bowel disease
  - Immaturity of absorptive systems
- Increased body losses
  - Starvation
  - Burns
  - Diabetes mellitus
  - Ketoacidosis
  - Diuretic treatment
  - Proteinuria
  - Hepatic disease
  - Intravascular haemolysis (for example, sickle cell anaemia)
  - Porphyria
  - Chelating agent therapy
  - Chronic blood loss
  - Parasitic infection
  - Dialysis
  - Exfoliative dermatitis
  - Excessive sweating
- Intravenous feeding

several of these predisposing factors. Some examples are listed in Table 1; in some instances there is no conclusive evidence of zinc deficiency (see above) but all constitute 'at risk states' and have been associated with markedly reduced plasma or serum zinc levels, some of which deserve comment.

Inadequate dietary intake. Protein-calorie malnutrition in the developing parts of the world is probably the most common cause of zinc deficiency, but Western populations may be at risk from a marginal zinc intake. This may be the case in vegans, vegetarians (Bodzy *et al.*, 1977), low socioeconomic groups subsisting on low meat diets (Hambidge *et al.*, 1972, 1976), and patients with chronic renal disease on low protein diets (Rose and Willden, 1972). Synthetic diets used in the treatment of children with inborn errors of metabolism and dietary intolerances require zinc supplements (Alexander *et al.*, 1974; Thorn *et al.*, 1978), and this may be the case for soya-based infant formulae although it has not yet been assessed. It is conceivable that the ingestion of texturised vegetable protein meat extenders and other novel protein sources, or calorie-controlled diets may be at risk. The need for fuller evaluation of feeding practices is stressed by the work of Walravens and Hambidge (1976) who demonstrated an improved growth rate in baby boys receiving standard formulae containing zinc supplements.

Malabsorption. Defective absorption of zinc may be secondary to the immaturity of its absorption systems, as may be the case in newborn babies especially if preterm (Dauncey *et al.*, 1977). Any individual with gastrointestinal disease is potentially at risk of developing zinc deficiency, particularly if the condition is long standing. Deficiency may result from intraluminal binding of zinc to high affinity ligands, impaired secretion of pancreatic ZBL, defective uptake into mucosa, reduced mucosal ZBL, or increased secretion into the intestinal lumen. The pathophysiological mechanisms which operate in the genesis of zinc deficiency in various disorders of the gastrointestinal tract present an important and challenging area for future research.

In 1973 Moynahan and Barnes made the important discovery that all the clinical manifestations of acrodermatitis enteropathica (AE) resolved strikingly with oral zinc treatment (Moynahan, 1974). This historic discovery undoubtedly added a major motivation and impetus to research concerned with zinc in health and disease states in man. Impaired ^{65}Zn absorption has been shown in AE (Lombeck *et al.*, 1975), and balance studies have shown that patients are in a net negative state with respect to zinc, and that this is accounted for by increased faecal losses (Aggett *et al.*, 1978). Although these observations suggest malabsorption of zinc, they do not define the pathogenesis of malabsorption. We have demonstrated a pronounced defect in the *in vitro* uptake of zinc in jejunal biopsies obtained from patients with AE, both when they are in remission and relapse (Atherton *et al.*, 1979). Thus the primary abnormality in AE may be defective zinc uptake into the enterocytes and the condition represents an addition to the known selective inborn errors of absorption (Harries, 1977). Recently preliminary evidence of defective zinc binding by duodenal juice of patients with AE has been reported (Casey *et al.*, 1978).

Increased body losses. Increased body losses may occur in a wide variety of conditions, as shown in Table 1.

Intravenous feeding. Intravenous feeding, particularly if prolonged, carries a risk of zinc deficiency. This is in part secondary to the variable but low content of zinc in the administered solutions (van Caillie *et al.*, 1978) and to the excessive urinary losses of zinc complexed with carbohydrates or amino-acids, or both (Freeman *et al.*, 1975). It is particularly likely to occur during an anabolic phase where there is an abrupt increase in body requirements and it is important to monitor zinc status during and after reintroduction of oral feeding (Fleming *et al.*, 1976).

Clinical manifestations of zinc deficiency

The variable and protean clinical manifestations of zinc deficiency are listed in Table 2. Anorexia, growth retardation, and impaired taste and olfactory sensation, are early features as is mood alteration. Most neurological features have been described in adults with induced zinc deficiency (Henkin *et al.*, 1975b); jitteriness and altered behaviour have been

Table 2 *Clinical manifestations of zinc deficiency*

Anorexia
Impaired taste and smell
Pica
Growth retardation
Hypogonadism
Impotence in renal dialysis patients
Depression, mood lability, impaired concentration
Intention tremor
Nystagmus
Dysarthria
Jitteriness
Photophobia, night blindness, blepharitis
Skin lesions (digits, perineum, parietal, nasolabial folds)
Paronychiae with monilial superinfection
Nails (growth arrest, loss, Beau's lines)
Hair growth arrest or alopecia
Delayed wound healing
Diarrhoea

reported in infants (Sivasubramanian and Henkin, 1978). Cutaneous signs range from a rough skin to a severe eczematous dermatitis affecting the digits, perineum, mouth, and nasolabial folds.

The biochemical consequences of zinc deficiency in human adults include reduced plasma alkaline phosphatase and lactate dehydrogenase activities, raised plasma ammonia, and increased plasma ribonuclease activity (Prasad *et al.*, 1978b).

Impaired night vision might be more associated with impaired retinol dehydrogenase activity (Huber and Gershoff, 1975) than with any specific effect zinc deficiency may have on retinol-binding protein synthesis (Carney *et al.*, 1976).

Impaired cell-mediated immunity with poor lymphoblast response, absent skin sensitivity reactions (Golden *et al.*, 1978), thymic hypoplasia (Golden *et al.*, 1977), and defective monocyte and polymorphonuclear leucocyte mobility have been associated with zinc deficiency and may contribute to the infections which occur particularly in patients with AE (Weston *et al.*, 1977).

In the pregnant rat even transient zinc deficiency results in an increased incidence of fetal resorption, stillbirths, and abnormalities of the CNS, skeleton, lung, urogenital tract, and palate in the offspring; moreover, the newborn rats tend to be of low birthweights with altered learning and behavioural patterns (Hurley and Mutch, 1973). The last features have also been described in rhesus monkeys (Sandstead *et al.*, 1978). The one abortion and the 2 congenital abnormalities reported in the 7 recorded pregnancies of 3 women with AE suggest that similar effects may apply to the pregnant human (Hambidge *et al.*, 1975). It has been speculated that the high incidence of anencephaly in some Middle Eastern countries may be the result of environmental zinc deficiency (Sever and Emanuel, 1973). Serum zinc levels in women having abnormal deliveries or low birthweight or preterm infants were lower than in women not experiencing such abnormalities (Jameson, 1976). A causal relationship was not established however.

Treatment of deficiency states

Zinc can be administered as a sulphate (22·5 mg (350 μmol) of elemental Zn/100 mg), acetate (30 mg (460 μmol) Zn/100 mg), or oxide (80 mg (1·2 mmol) Zn/100 mg) salts. Zinc gluconate preparations are also used. In some individuals the salt, particularly the sulphate, can be irritant to the gastrointestinal tract and in these circumstances the zinc salt may be taken with a meal or capsulated preparations may be better tolerated; but zinc is less efficiently absorbed with meals and from capsules (Oelshlegel and Brewer, 1977). These zinc salts have a wide therapeutic index and their doses should be adjusted according to the clinical response. In deficiency states an initial daily dose of 15 μmol elemental Zn/kg is given orally, or 5 μmol/kg IV. For maintenance IV therapy 2 μmol/kg is given daily at first. Larger oral doses are necessary in patients with AE. Plasma zinc and copper should be monitored frequently in these circumstances.

Zinc salts have also been used in the treatment of gastric ulcers (Frommer, 1975), rheumatoid arthritis (Simkin, 1976), and acne (Michaëlsson *et al.*, 1977). These applications await further evaluation and the consequences of prolonged oral zinc administration (see below) indicate that such use of zinc should be undertaken cautiously.

Toxicity

Zinc salts are usually well tolerated, but toxic effects have been associated with oral ingestion of elemental zinc (Murphy, 1970), zinc sulphate capsules (Moore, 1978), the use of water from galvanised containers for drinking (Brown *et al.*, 1964) and home dialysis (Gallery *et al.*, 1972), sucking zinc alloy toys (Chunn, 1973), prolonged oral zinc supplements (Prasad *et al.*, 1978a), and intravenous overdosage (Brocks *et al.*, 1977). Symptoms include anorexia, nausea, vomiting, lethargy, dizziness, diarrhoea, and bleeding gastric erosions; raised serum amylase and lipase were noted by Murphy (1970), and copper deficiency with hypochromic anaemia with reduced plasma copper concentrations have been reported after prolonged treatment with oral zinc. Intravenous overdosage has been associated with acute renal failure and death. Contact dermatitis to zinc salts (Freeman, 1942) and zinc allergy in diabetics on zinc insulin preparations have also been described (Feinglos and Jegasothy, 1979).

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Coronary arterial lesions and myocardial necrosis in stillbirths and infants

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SUMMARY In a detailed study of the coronary arterial tree and myocardium in 256 stillbirths and infants, abnormalities of the coronary arterial tree were noticed in 79 infants, and necrotic lesions of the myocardium in 111 infants. Of the 79 infants with arterial lesions, 70 had associated myocardial necrosis or scarring, or both; the group with coronary arterial lesions, therefore, accounted for the majority of cases with myocardial damage.

The myocardial lesions varied from small zones of subendocardial damage, to larger 'geographical' zones of necrosis scattered haphazardly through the myocardium, and a small group where massive necrotic lesions of the papillary muscles were present. While the coronary arterial lesions were associated with all three patterns, they were particularly found in association with the 'geographical' and papillary muscle changes.

The coronary arterial lesions varied from zones of acute focal, medial necrosis to severe proliferative intimal lesions and medial defects, with a distinct progression of changes from the acute to the more established lesions. The coronary arterial lesions were seen most commonly in association with conditions that could produce severe hypoxia, and it is argued that they result from hypoxia. It is suggested further that the myocardial damage, so commonly associated with the coronary arterial lesions, could compromise the ability of the hypoxic infant to respond to such an insult.

The coronary arterial lesions seen in this group of young infants could offer one explanation for the later development of a variety of other pathological conditions seen in adolescents and young adults.

In 1946 Dock described proliferative intimal changes in the coronary arterial tree of infants and young adults, and his findings were confirmed and extended by many others (Fangman and Hellwig, 1947; Minkowski, 1947; Lober, 1953; Levene, 1956; Schornagel, 1956; Moon, 1957; Robertson, 1960; Vlodaver *et al.*, 1967). Gruenwald (1949) reported necrotic lesions in the coronary arteries of 21 stillbirths and infants and he commented on their association with small foci of myocardial necrosis. He was unable, however, to follow their natural history.

Several reports describe myocardial necrosis in newborn babies and infants. Esterly and Oppenheimer (1967), and Franciosi and Blanc (1968) found evidence of myocardial necrosis in infants with a variety of congenital malformations of the heart and great vessels. Berry (1967), in a review of cases of myocardial necrosis occurring in infants and young children, reported several infants with myocardial necrosis, one of whom showed evidence of coronary artery occlusion. Gault and Usher (1960) described a neonate with coronary thrombosis and myocardial infarction complicating birth asphyxia. Bucciarelli *et al.* (1977), in a study of acquired tricuspid insufficiency in the newborn, found large areas of necrosis in the anterior papillary muscle of one such infant, but did not mention any changes in the coronary vessels.

In an earlier paper (de Sa, 1977), a wide spectrum of myocardial lesions was found in a group of immature hypoxic infants whose lives had been sustained by prolonged assisted ventilation. In that report, destructive lesions of the smaller, intramural branches of the coronary arterial tree were noted but were not elaborated on. The present report is

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based on a detailed study of the coronary arterial tree in 256 stillbirths and infants. The presence of non-flammatory, necrotic, and degenerative lesions of the coronary arterial tree is described and their close association with myocardial necrosis and scarring is stressed.

Materials and methods

The necropsy records of the McMaster University Medical Centre provided most of the case material, but additional material was obtained through the co-operation of colleagues in St Joseph's and Henderson General Hospitals and the forensic pathology unit, Hamilton. The hearts and coronary vessels of 82 fresh stillbirths, 86 first-week neonatal deaths, 33 other neonatal deaths ages <28 days, 24 infants requiring prolonged ventilation (de Sa, 1977), 13 cases of sudden infant death syndrome, and 18 other infants age <one year were studied. In most instances the necropsies were conducted personally or the heart was available for a detailed study. Apart from the blocks of myocardium selected for routine histology, samples of myocardium were available in the reserve stocks taken at the time of necropsy. Even in retrospect, therefore, a detailed examination could be made.

Hearts with congenital malformations of the septum, great vessels, or valves were excluded. Multiple blocks of myocardium, including endocardial and epicardial surfaces, were embedded in paraffin and each block was studied at several different levels.

The numbers of blocks studied depended on the size of the heart. However, in all cases, at least 3 blocks were taken through the free wall of both ventricles, and these included the papillary muscles and atrioventricular grooves. In addition, at least 3 blocks were sampled through the entire thickness of the interventricular septum, including both anterior and posterior epicardial surfaces. Separate blocks were taken to include the left and right coronary arteries near their respective aortic ostia. In the larger hearts, further transversely orientated blocks were taken through an area of myocardium bounded posteriorly by the opening of the coronary sinus and extending anteriorly to include membranous interventricular septum and adjacent muscularis for a distance of approximately 0·3 cm. These blocks included the atrioventricular node, bundle of His, and both bundle branches. Sections were cut through these blocks at several levels and stained with a variety of standard histological techniques, as appropriate.

In some cases, blocks of formalin-fixed tissue were processed for ultrastructural study after selecting the areas under a Leitz dissecting microscope. These blocks were embedded in epon, and sections were cut at 1μm and stained with toluidine blue. Specific areas were chosen from these blocks and sectioned on an LKB ultramicrotome and stained with lead citrate and uranyl acetate, and examined on a Philips 300 electron microscope.

Results

Myocardial lesions. In this series, myocardial lesions (including acute necrosis, replacement with granulation tissue and/or scarring) were found in 111, and coronary arterial lesions (to be described below) were found in 79 (31 %) of the 256 infants. However of the 79 infants with coronary arterial lesions, 70 (89 %) had associated myocardial lesions. Infants with coronary arterial lesions, while only constituting a minority of the infants studied, accounted for most cases (70 of 111 or 63 %), with histologically detectable myocardial damage.

The myocardial lesions that were identified were similar in their range and severity to those identified as part of the considerably smaller, earlier series (de Sa, 1977). Generally focal band-like areas of necrosis or scarring were present (83 of 111 infants). These lesions were most often seen in the subendocardial areas of the myocardium (Fig. 1) but not exclusively so. Next in frequency (29 of 111 infants) were irregular geographical areas of necrosis or scarring, scattered haphazardly through both ventricles often associated with small collars of surviving myocardium around intramural vessels (Fig. 2). Finally large areas of necrosis or scarring affecting appreciable areas of papillary muscles were identified in 16 of the 111 infants (Fig. 3). As Table 1 shows, several infants had more than one pattern of necrosis. Furthermore, it is clear that while coronary arterial damage was associated with all three patterns of injury, it was more often associated with the larger lesions.

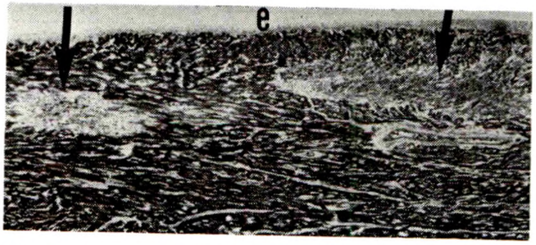

Fig. 1 *Small zones of subendocardial fibre necrosis (arrows) are seen in the heart of this 14-day-old infant, 34 weeks' gestation. Lesion on left is somewhat more advanced. Endocardial surface is indicated by 'e'. Gomon's trichrome (GT) × 150.*

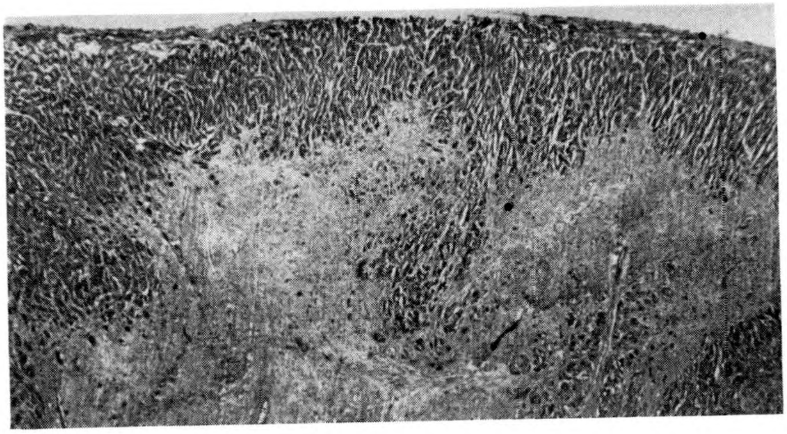

Fig. 2 *Large, pale-staining 'geographical' zones of scar tissue, replacing areas of previous myocardial necrosis are seen in this section through the interventricular septum of a 102-day-old infant, maintained on prolonged ventilation. GT* × 25.

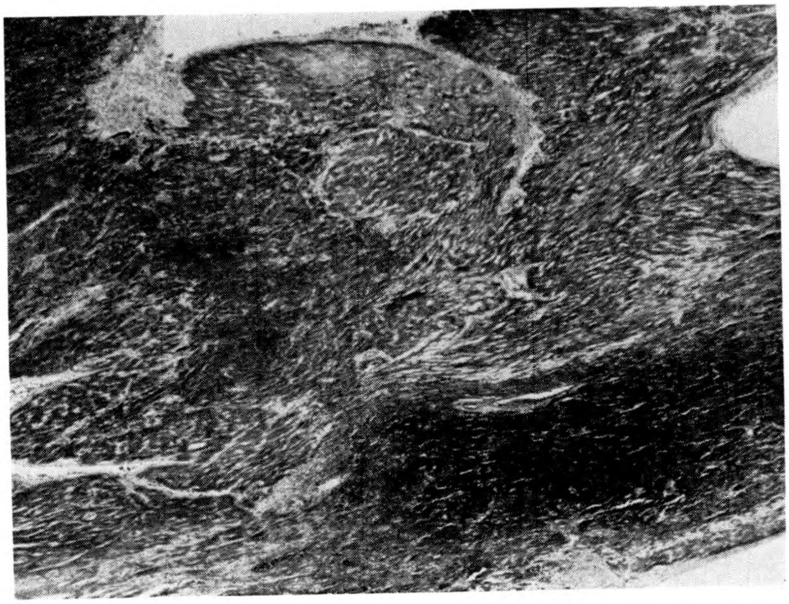

Fig. 3 *Section shows massive acute necrosis (darkly stained) occurring in the posterior papillary muscle of the mitral valve of a 5-day-old infant, 29 weeks' gestation, born after a pregnancy complicated by abruptio placentae. GT* × 180.

Table 1 *Myocardial necrosis and coronary arterial lesions*

Type of myocardial lesion	*Infants with coronary arterial lesions (n = 79)*	*Infants without coronary arterial lesions (n = 177)*	*Total no. of myocardial lesions (n = 256)*
Focal	48	35	83
Geographical	17	12	29
Papillary muscle	11	5	16
None	9	136	145

Histological findings in the coronary vessels

The impetus for the present study was provided by a chance observation of a section through an epicardial petechial haemorrhage in a one-day-old infant of 28 weeks' gestation, which showed an area of obvious medial necrosis in the anterior descending coronary artery. In adjacent sections disruption of the internal elastic lamina, early thrombus formation, and imminent rupture of the wall were demonstrated (Fig. 4).

Early necrotic lesions appeared as small areas of smudging of medial cellular detail. They were seen to greatest advantage near areas of perivascular petechial haemorrhages, associated with the rupture of small capillaries in connective tissue around the larger vessels, both on the surface of the heart and intramurally. The lesions were readily seen in 1 μm sections (Fig. 5). In many of these cases, step sectioning through the block showed focal micro-

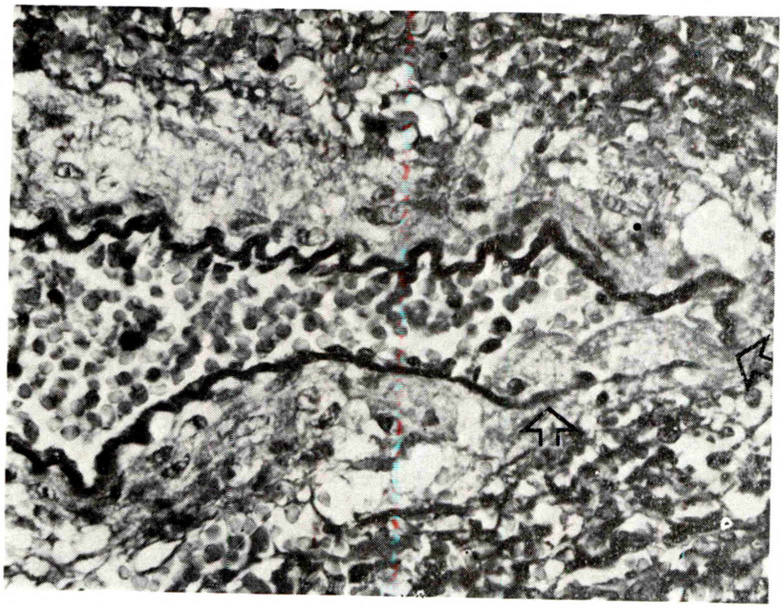

Fig. 4 *Disruption of the internal elastic lamina (zone between arrows), is seen in this section, through the anterior descending coronary artery of a 2-day-old infant of 28 weeks' gestation. Note globular, amorphous masses of thrombus present in relation to area of destruction of the internal elastic lamina. Haematoxylin, alcian green, elastic, Van Gieson (HAEVG)* × 1000.

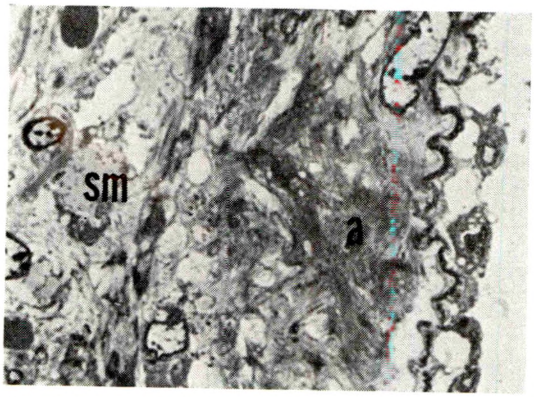

Fig. 5 *Plastic-embedded section through an area of very early medial necrosis in an infant of 31 weeks' gestation, 2 days' postnatal age. Media show an acellular area 'a' where the smooth muscle cells are destroyed and replaced by an amorphous fibrillary mass. Note also vacuolated smooth muscle cells 'sm' scattered through the wall. Toluidine blue (TB) × 2200.*

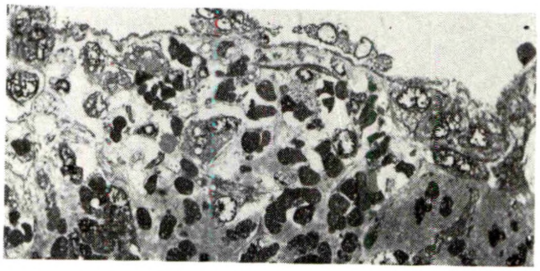

Fig. 6 *Plastic-embedded section from the same vessel as in Fig. 5. Luminal surface is in upper segment of figure and several areas of denudation of the intimal cells are present. Striking feature however is presence of large numbers of darkly-stained red cells present within wall of the artery. These red cells dissect between and separate small groups of smooth muscle cells. In this section no break in the internal elastic lamina was noted. TB × 1200.*

dissection (Fig. 6) with infiltration of red cells through and among degenerate muscle cells of the media. The extent of muscle necrosis in affected vessels varied considerably, from large geographical defects in the media to exquisitely selective focal loss of muscle cells (Figs 7 and 8). A striking feature was the absence of any significant inflammatory reaction and the necrotic lesions were not due to a primary arteritis.

Accompanying the loss of muscle cells in the media, there was aneurysmal dilatation and microdissection resulting in the formation of false aneurysms. In one infant it was possible to trace the development of a false aneurysm (Fig. 9) through the stages of muscle necrosis, microdissection, and enlargement until it eventually disappeared.

Small, nonocclusive thrombi were quite commonly present in the lumina of damaged vessels (Fig. 10). In these infants the small peripheral vessels within the myocardium contained small thromboemboli

(Fig. 11), and, occasionally, early organisation of embolus and its incorporation below the endothelium of small vessels could be identified.

The spectrum of changes described in the preceding paragraphs were more commonly seen in the stillbirths and younger infants in the series, and were found more readily in hearts with endocardial and epicardial petechial haemorrhages. The affected vessels varied in size and the largest ones, in this particular series, were the first major branches of both right and left coronary arteries (anterior descending branch of left coronary artery, lateral branch of right coronary artery). In this series acute necrotic lesions of the main right and left coronary arteries were not identified.

The older infants in the series showed a somewhat different spectrum of changes. The least obvious lesions consisted of small scars of media, with

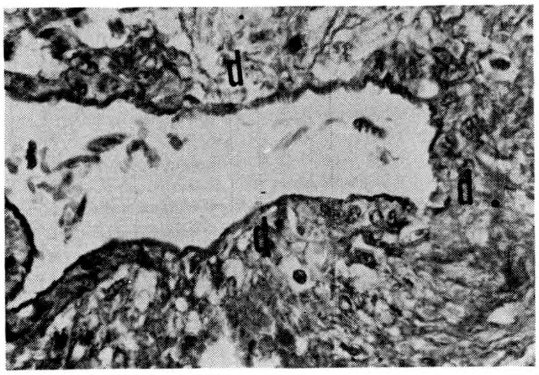

Fig. 7 *Section through a branch of the circumflex artery, 35 weeks' gestation, 3-day-old infant, showing large defects 'd' in the media. Note absence of any inflammatory reaction. HAEVG, × 700.*

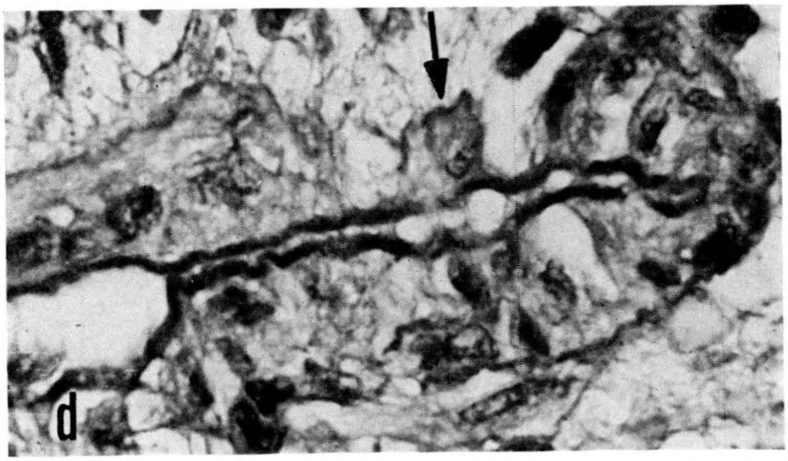

Fig. 8 *Same case as Fig. 7 taken from a lateral branch of the anterior descending coronary artery, showing single surviving smooth muscle cell of the media (arrow) and also a larger defect 'd' in the medial musculature. HAEVG, × 1600.*

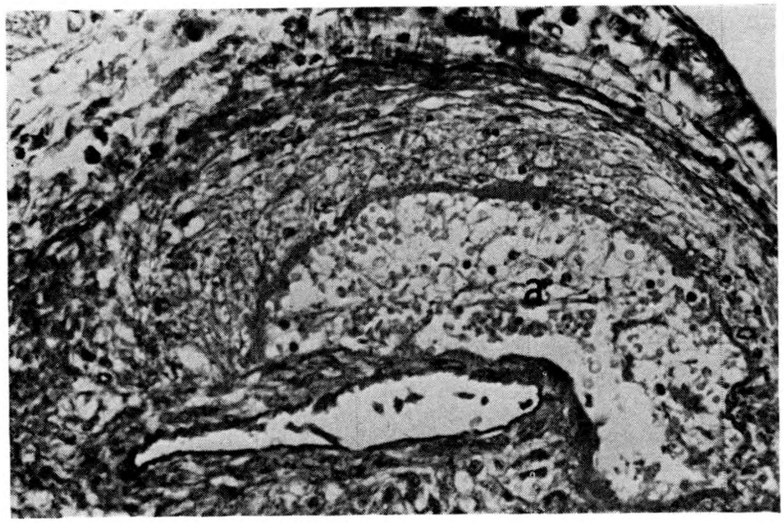

Fig. 9 *Posterior interventricular branch of the right coronary artery in a 39-week-gestation infant aged 9 days. A large false aneurysm of the wall 'a' is shown. In serial sections its development from areas of microdissection could be traced. HAEVG, × 450.*

excessive accumulation of acid mucopolysaccharide and fragmentation of the elastica (Fig. 12). In many of the older infants different stages in the organisation of thromboemboli within peripheral branches were present, amounting in some instances to obliteration of the lumen (Fig. 13). There was also evidence of progressive recanalisation of the vessel lumen (Fig. 14) and the affected vessels showed very obvious distortion of their architecture (Fig. 15). Many severely damaged vessels, with cellular intimal plaques overlying areas of pronounced medial hypoplasia were present (Fig. 16).

In many of the older infants prominent intimal

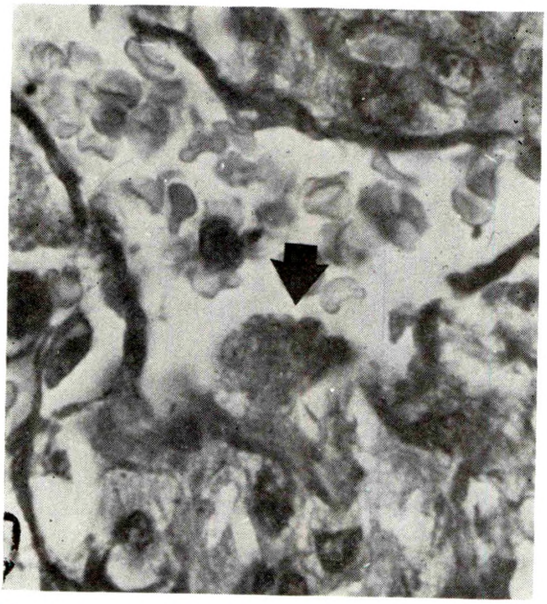

Fig. 10 *Serial section from same vessel as Fig. 6, showing a small mushroom-like thrombus protruding into the vascular lumen (arrow). HAEVG,* × *4000.*

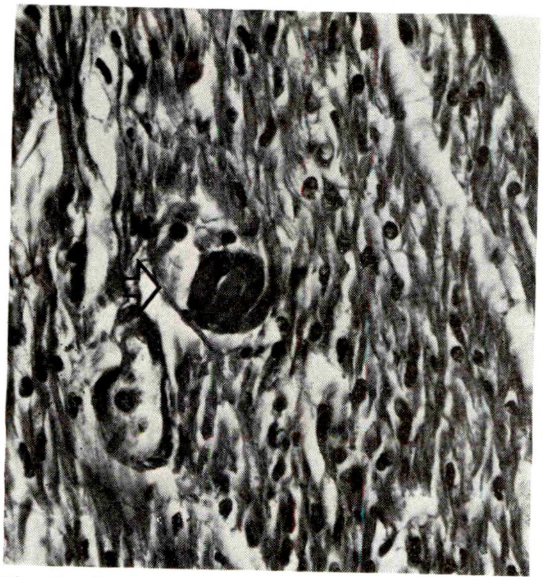

Fig. 11 *Intramural thromboembolus (arrow) in 35-week-gestation infant aged 5 days. Embolus is attached to the vessel wall and in other serial sections an early stage of endothelialisation was evident. Martius scarlet blue (MSB)* × *1000.*

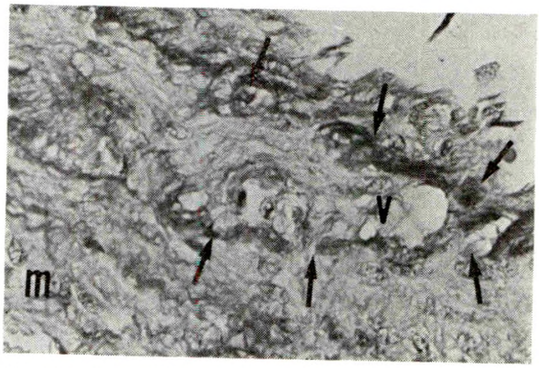

Fig. 12 *Circumflex artery in an infant of 26 weeks' gestation, 42 days' postnatal age. There is obvious splitting and reduplication of the internal elastic lamina (arrows). Large vacuoles 'v' staining faintly with alcian green, indicate presence of abnormal amounts of acid mucopolysaccharides. Note also the defects in the medial elastic tissue 'm'. HAEVG,* × *700.*

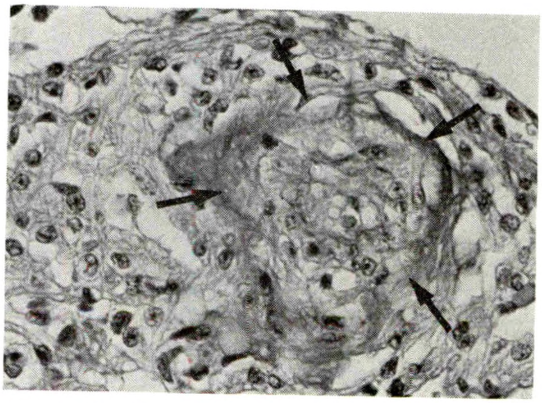

Fig. 13 *Section through base of the anterior papillary muscle of the mitral valve in a 3-month-old infant, born at 29 weeks' gestation, who presented as a 'sudden infant death'. An obliterated intramural vessel is outlined by arrows. Serial sectioning traced its origin from an intramural artery shown in Fig. 14. HAEVG,* × *1000.*

proliferation was noted in the surface vessels. There was disruption of the internal elastic lamina, irregular smooth muscle proliferation, and excessive deposits of collagen and elastic tissue in the intima (Fig. 17).

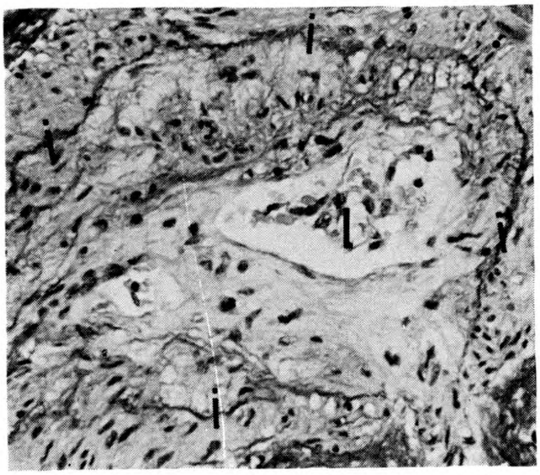

Fig. 14 *Same infant as in Fig. 13. Parent vessel of lesion shown in Fig. 13 is seen. There is obvious disorganisation of the architecture. Internal elastic lamina is outlined 'i' and indicates the approximate size of the original vessel lumen. New vessel lumen 'L' is considerably narrower. These appearances were interpreted as being due to recanalisation of the vessel after obliteration. HAEVG,* × *700.*

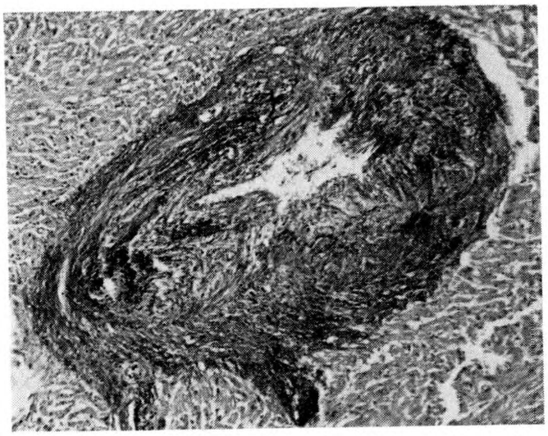

Fig. 15 *Complete destruction of architecture is seen in this section from the right ventricle of a 6-month-old infant, born at 39 weeks' gestation with an omphalocele which was repaired, but who required prolonged ventilation. Landmarks of the vessel wall are replaced by darkly-staining bands of elastotic scar tissue. Elsewhere in this section numerous normal vessels were found. HAEVG,* × *220.*

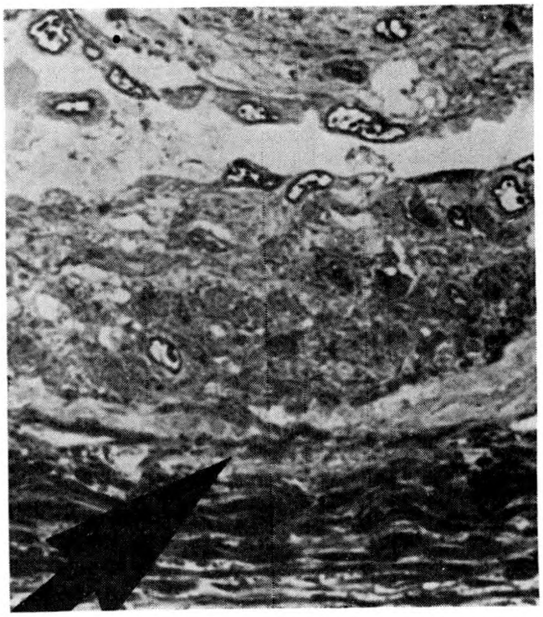

Fig. 16 *Intimal plaque in an intramural vessel from an infant age 99 days, born at 26 weeks' gestation, showing the cellular nature of the lesion and the obvious atrophy of the media (arrowed) under the point of maximum thickness of the plaque. Plastic-embedded, TB,* × *4000.*

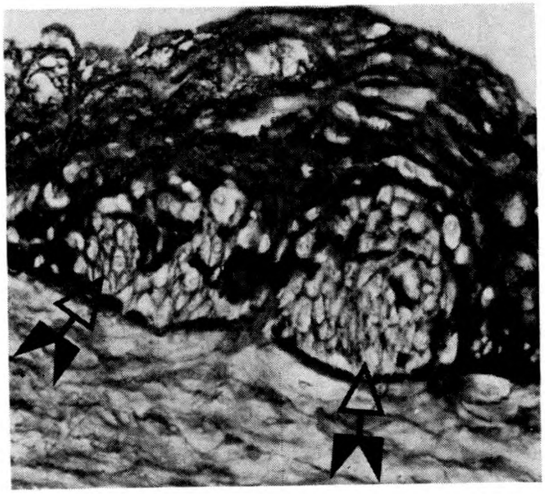

Fig. 17 *Small intimal plaque in anterior descending branch of coronary artery in 4-month-old 'sudden infant death'. Smooth muscle nodules (arrows) are present just above the internal elastic lamina, which shows up as an irregularly reduplicated layer. Aldehyde-fuchsine,* × *1000.*

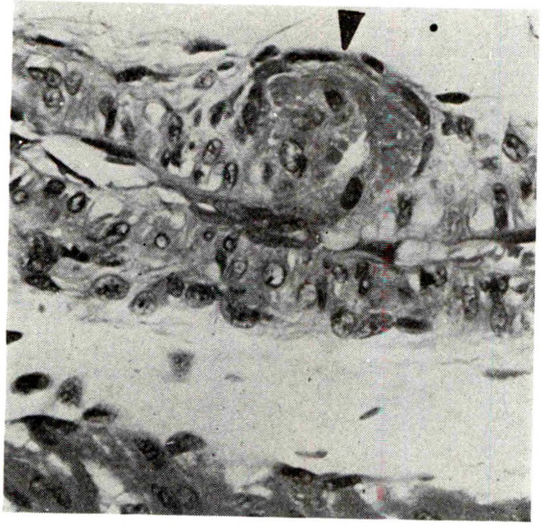

Fig. 18 *Intramural myocardial vessel from 2-month-old infant born at 40 weeks' gestation with severe birth asphyxia and with evidence of brain damage. A globular lesion (arrow) filled with fibrillary material, that stained positively for fibrin (not shown), is present. Media at this point of the vessel appear irregular and much less cellular than on the opposite side of the vessel wall section. Lesion was interpreted as a healed false aneurysm. Haematoxylin and eosin (H & E), × 1000.*

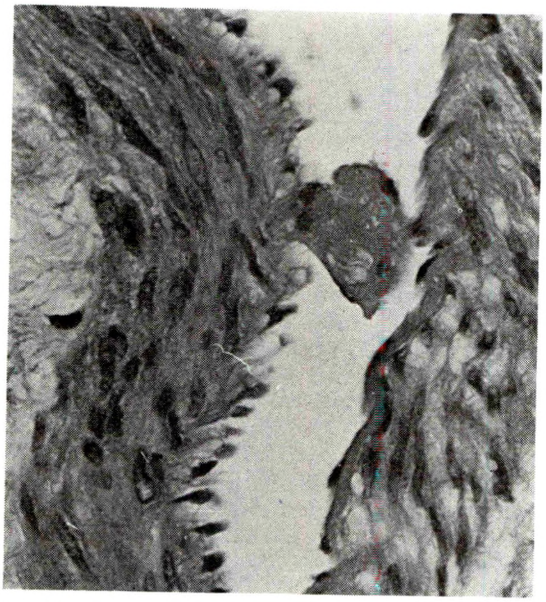

Fig. 19 *Organised, pedunculated, thrombus in an infant aged 32 days, born at 26 weeks' gestation. Lesion was seen in a branch of the circumflex artery. H & E, × 1000.*

In some of the older infants occasional zones of acute medial necrosis in both surface and intramural vessels could still be identified. This finding gave substance to the speculation that the degenerative changes seen in the older infants represented the end results of acute lesions seen in younger ones.

Some miscellaneous lesions were also identified. In one infant a rounded globular lesion contained fibrinous material, and was interpreted to be a healed false aneurysm (Fig. 18). Polypoidal structures in some larger vessels almost certainly represented organised thrombi (Fig. 19). Many of the smaller intramural vessels showed the presence of prominent foamy endothelial cells projecting into the lumen, and these were interpreted as representing a reaction to previous emboli.

Ultrastructural studies

In certain, selected cases, the 1 μm thick sections allowed the identification of zones of vacuolated smooth muscle cells in the walls of vessels which were severely damaged (Fig. 20) and representative samples from these areas were taken for ultrastructural studies. The cells themselves contained abundant lipid vacuoles, closely associated with

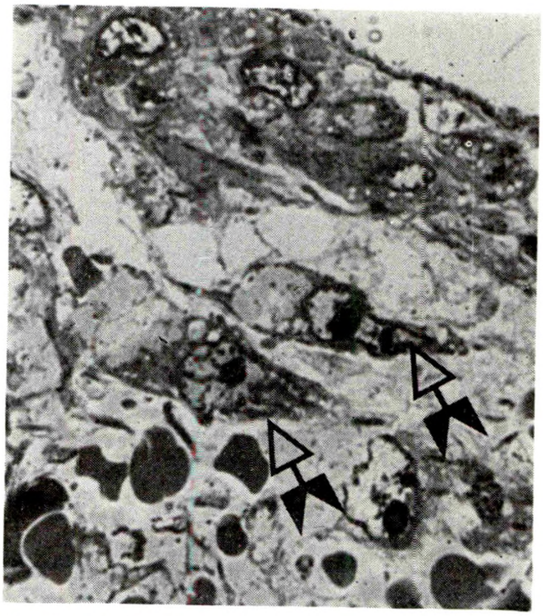

Fig. 20 *Section through an epicardial petechial haemorrhage from a stillborn infant of 42 weeks' gestation after a pregnancy complicated by abruptio placenta. Outer layers of media show the presence of grossly distorted smooth muscle cells (arrows), with numerous lipid vacuoles in the cytoplasm. Plastic embedded section, TB × 4000.*

granular endoplasmic reticulum, and many of the lipid vacuoles appeared to contain complex convoluted inclusions resembling myelin figures (Fig. 21). It was thought that these changes represent very early evidence of smooth muscle cell damage.

Associated clinical features. The frequency with which destructive lesions of the coronary arterial tree were found is shown in Table 2, and the high incidence in stillbirths, early neonatal deaths, infants maintained on prolonged ventilation, and sudden infant deaths is obvious. In the whole series nearly one-third of the infants had evidence of coronary arterial lesions.

The complications of pregnancy and postnatal life in the younger infants in this series are shown in Table 3. It can be appreciated that infants with necrotic and degenerative lesions of their coronary vessels were often associated with conditions that could lead to hypoxia both *in utero* and in postnatal life. In particular antepartum haemorrhage, fetal bradycardia, postnatal apnoeic attacks, respiratory distress syndrome, intraventricular haemorrhage, and any indication for prolonged ventilation were important associations.

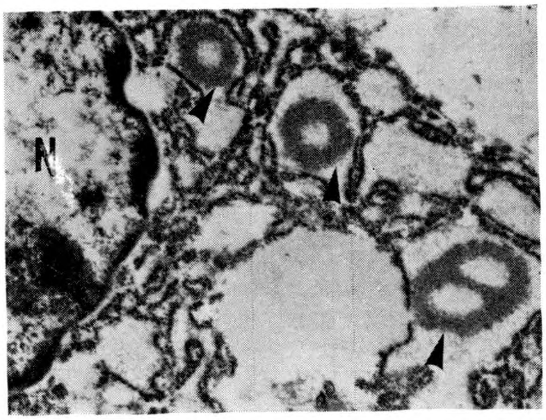

Fig. 21 *Electron micrograph of the foamy smooth muscle cells seen in Fig. 20, showing the numerous myelin-like figures in lipid vacuoles in the cytoplasm. N = nucleus. Uranyl acetate and lead citrate;* × *20 000.*

Table 2 *Incidence of coronary arterial lesions*

	Total ($n = 256$)	*Affected* ($n = 79$)
		No. (%)
Fresh stillbirths	82	20 (24)
First week neonatal deaths	86	24 (28)
Infants on prolonged ventilation	24	22 (92)
Other neonatal deaths	33	5 (15)
Sudden infant death syndrome	13	5 (38)
Other infants	18	3 (17)

Table 3 *Gestation, birthweight, and complications of pregnancy, delivery, and neonatal life*

	Infants with arterial lesions ($n = 79$)	*Infants without arterial lesions* ($n = 177$)
Gestation (weeks)		
28 or less	18	59
29–37	37	77
38–41	16	23
>41	2	6
Not known	6	12
Birthweight (g)		
<1000g	16	29
1001–1500	16	21
1501–2000	13	46
2001–2500	10	31
2501–3000	8	19
3001–3500	9	16
>3500	4	6
Not known	3	9
Mode of delivery		
Vertex	36	86
Breech	19	37
Caesarean	12	22
Other	—	4
Not known	12	28
Complications of pregnancy, delivery, or neonatal life.*		
Antepartum haemorrhage	32	36 ($P<0\cdot01$)
Maternal hypertension	14	29
Maternal diabetes mellitus	4	3
Prolonged rupture of membranes	16	38
Fetal bradycardia	58	69 ($P<0\cdot001$)
Meconium staining of liquor	28	62
Apgar score <6 at 1 min/5 min	56	85
Apnoeic attacks	44	56 ($P<0\cdot001$)
Respiratory distress	36	49 ($P<0\cdot01$)
Interstitial emphysema/pneumothorax	21	29
Bronchopulmonary dysplasia	41	48 ($P<0\cdot001$)
Pneumonia	6	14
Intraventricular haemorrhage	41	68 ($P<0\cdot05$)

*Most infants appear more than once.

In view of this apparent association with hypoxia, the clinical histories of the older infants (*not* maintained on prolonged ventilation) and the 'cot deaths' were reappraised. In particular, evidence of hypoxic episodes or conditions predisposing to hypoxia were searched for. These were present in 5 of the 13 'cot deaths' and in 6 of the 18 older infants (Table 4). Four of the 13 'cot deaths' were stated to have weighed 2500 g or less at birth. In 3 infants this was associated with maternal hypertension. In the remaining low birthweight infant no other associated anomaly of pregnancy was described. In the fifth 'cot death' there was a history of vaginal bleeding 3 days before delivery. In the 6 older infants, with anomalies of pregnancy and postnatal life, the clinical records were even less detailed than in the 'cot deaths'. Three were stated to have had apnoea at birth; 2 infants were said to have been 'premature' but no further details were given. One infant was

Table 4 *Evidence of perinatal hypoxia (sudden infant deaths and older infants)*

Infants	*Sudden deaths*	*Older infants*
With coronary arterial lesions	3 of 5	2 of 3
Without lessions	2 of 8	4 of 15

Table 5 *Comparison of coronary, renal, and adrenal arterial lesions*

Infants (n = 256)	*Infants with arterial lesions*	
	Renal	*Adrenal*
With coronary arterial lesions (n = 79)	6	8
Without coronary arterial lesions (n = 177)	12	8

delivered by the breech with severe birth asphyxia, and also showed evidence of thalamic and brain stem neuronal loss at necropsy (at age 3 months). She was known to have had severe cerebral damage during life.

Findings in other vessels

Surprisingly, necrotic and proliferative changes of the variety described in the coronary arterial tree were not seen as commonly in the renal or adrenal vasculature (Table 5). When present in the microvasculature in these areas, they were almost invariably associated with thromboemboli associated with 'high placement' of an umbilical arterial catheter within the aorta, and several of these infants have been described elsewhere (Tyson *et al.*, 1976). In 5 infants the thromboemboli were probably derived from other sources: in 3 infants, fibrinous vegetations were present on both tricuspid and mitral valves. In the other 2 infants, thrombi were noted in pulmonary venules in association with bacterial pneumonitis.

Discussion

It has been known for a long time that the adequacy of the fetus' and infant's response to asphyxia to a great extent depends on the integrity of the cardiovascular system (Cross, 1966). If the cardiovascular system is damaged the fetus is compromised. In recent years interest in the myocardial function and reserve in perinatal hypoxia or asphyxia has been growing, and there is abundant evidence that in many instances the myocardium is affected in states of severe hypoxia (Burnard and James, 1961; Rowe and Hoffman, 1972; Rowe *et al.*, 1978). While this may reflect direct myocardial damage in hypoxia (de Sa, 1977), the possibility that damage to the coronary arterial tree may be an important factor does not appear to have been considered, and the earlier observations of Gruenwald (1949) have passed unnoticed. Yet it is clear, that in cases where there is frank myocardial necrosis (Bucciarelli *et al.*, 1977; de Sa, 1977) vascular lesions should be considered and sought for.

The data presented in this report show that coronary arterial lesions, albeit of a focal nature, are common in newborn infants, and that they are associated with myocardial necrosis. Owing to their focal nature, the arterial changes are not always easy to find and can be missed.

It is unlikely that the acute arterial lesions, described in this series of infants, represent the effects of resuscitation measures such as external cardiac massage. Not all our infants (with acute necrotic lesions) were resuscitated by this manner. While it is true that acute lesions were often more readily identifiable in surface vessels, many intramural vessels had similar changes. If it is suggested that the deep intramural vessels were damaged by external trauma, the insult must have been capable of producing exquisitely selective loss in the media of many vessels of varying calibre, while sparing many larger surface vessels and avoiding gross contusions of the myocardium. It is difficult to imagine such a model.

A far more convincing case can be made for the view that the many different arterial lesions seen in this small series of infants form part of a closely related spectrum. The sequence of events would include damage to the media, and in particularly severe cases to the intima, with the development of nonocclusive thrombi. Emboli could lodge in distal intramural vessels with varying degrees of myocardial damage. Repair of the initial vascular damage could explain the development of irregular medial scarring, with or without aneurysmal formation, and the striking intimal lesions seen in the intramural vessels could be traced to the organisation of thromboemboli. Such a sequence of events is known to occur in the vessels of other organs of humans (Salyer *et al.*, 1974; Sevitt, 1976; Tyson *et al.*, 1976), and animals (Allison *et al.*, 1967).

If the sequence of events outlined above is a correct interpretation, some of the earlier statements regarding 'remodelling' of the coronary arterial tree during growth of the fetus and infant need to be reassessed (Robertson, 1960; Ungar, 1965). During this study, numerous intramyocardial arteries were identified and examined closely. Most of them were perfectly 'normal' histologically without the evolution of longitudinal muscle bundles and other changes described by Ungar (1965). In the present series where deviations from the textbook 'normal' were identified, they were seen to be focal in nature and were often in close juxtaposition with 'normal'

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vessels of comparable calibre. As shown in Table 1 they were also often associated with myocardial lesions. One is tempted to agree with Wilens (1951) that most, if not all, intimal changes in any artery are due to pathological processes, and intimal changes in 'remodelled' vessels may be viewed in a similar fashion.

In this series there does not appear to be any relationship between the presence of coronary arterial lesions and a particular period of gestation or range of birthweight. It is easier to relate the lesions to the complications of pregnancy and postnatal life, and in particular to the likelihood of hypoxia or asphyxia that appears to represent the one factor common to them all.

It is well known that in infants dying from intrapartum asphyxia, epicardial and other serosal petechiae are common pathological findings at necropsy (Morison, 1970). The acute coronary arterial lesions presented in this paper were most readily identified in those hearts with epicardial petechiae, as Gruenwald (1949) pointed out earlier. In fact, what is thought to represent the very earliest evidence of arterial wall damage was seen near areas of ruptured, periarterial, epicardial capillaries. It is possible that some of the periarterial capillary vessels function as *vasa vasorum*. Certainly, retrograde injection of barium/gelatin mixtures into the ascending aorta with filling of the aortic sinuses and main coronary arteries delineate a delicate capillary network around the main coronary vessels and their larger branches (de Sa, unpublished observations). Rupture of these *vasa vasorum* could then produce the appearance of perivascular, epicardial petechiae. This, in turn, could lead to focal medial necrosis of the arterial wall, which could initiate the postulated sequence of events in the arterial wall.

Morison (1970) suggested that the serosal petechial haemorrhages seen at necropsy, in cases of intrauterine and intrapartum asphyxia associated with antepartum haemorrhage, were related to a great increase in the perfusing pressure in serosal capillaries. It is well known that in other situations an acute, rapid rise in blood pressure (as in the 'malignant' phase of hypertension) may be accompanied by evidence of bleeding due to destruction and rupture of the microvasculature (Goldby and Beilin, 1972). In experimental models, these areas of destruction are associated with fibrinoid necrosis (Allison *et al.*, 1967; Eto *et al.*, 1978). Similar changes are present in human material (Hughson and McManus, 1978). It is also known that in the human infant, one initial response to hypoxia or asphyxia is a sharp rise in blood pressure that may be related to catecholamine release (Dawes, 1968). It is permissible, therefore, to argue that in the asphyxiated baby a sharp rise in blood pressure, occurring as a reaction to the initial insult, may produce the rupture of epicardial vessels (Fig. 22).

For this explanation to be likely, however, it is necessary to explain the relative sparing of the visceral circulation (represented in this paper by the renal and adrenal vessels), for if the coronary vasculature is damaged by an episode of hypertension in response to an acute asphyxial insult, it would appear logical to expect lesions to be present in other viscera as well. The paradox can be explained only if it is postulated further that the splanchnic viscera, such as the adrenals and kidney, are 'protected' from the hypertension by a selective vasospasm. Such an explanation would be analogous to the discrepancy in the state of the arterial tree in the kidneys in cases of hypertension associated with unilateral renal artery stenosis. Here it is known that in the kidney supplied by the stenotic artery the arteries rarely show evidence of fibrinoid necrosis, while the arteries of the 'exposed' contralateral organ are severely affected (Heptinstall, 1966). One would expect that such a 'protective' vasoconstriction, while sparing the arteries, could make the organ prone to ischaemic damage. The association of haemorrhagic necrosis of the adrenal gland in stillbirths and infants with severe hypoxia/asphyxia *in utero* is well documented (de Sa and Nicholls, 1972), and presumably represents an example of this phenomenon.

It is possible, that if the initial asphyxial episode is severe and acute, and if the pressor response is pronounced there may be a considerable hazard posed to the fetus or newborn infant. It would be possible to construct a vicious cycle with a pressor

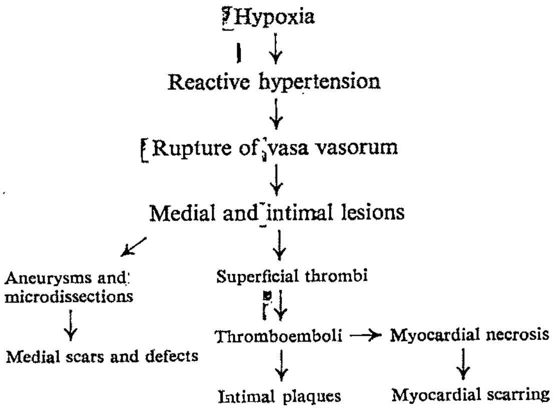

Fig. 22 *Suggested scheme for the development of necrotic and degenerative lesions of the coronary arterial tree in infants.*

response to hypoxia or asphyxia damaging the coronary arterial tree and affecting the myocardium secondarily. The damaged myocardium would be unable to respond adequately to the demands placed on it by the original insult, thereby deepening the metabolic complications of the asphyxia. Finally, poor coronary perfusion due to the myocardial damage (de Sa, 1977) would aggravate any original myocardial insult. If such vicious circles exist, extremely complex and severe anomalies of cardiac function could be expected. It was of considerable interest that at least some of the 'cot deaths' had myocardial and coronary arterial lesions strikingly similar to those infants with a well documented history of prolonged hypoxia. In fact, in some of these infants the clinical records suggested that hypoxic episodes had taken place. The findings are consistent, therefore, with some of the more recent views regarding the aetiology of 'cot (crib) deaths' (Naeye, 1973).

It is worth stressing the occurrence of coronary arterial changes in the newborn infant, irrespective of whether or not the pathogenesis of the lesions is known. They represent a serious hazard and may even help to explain how certain unusual lesions of the coronary arterial tree develop. Cases of medial calcification of the coronary vessels (Witzleben, 1970), occlusive fibroelastosis (MacMahon and Dickenson, 1967), coronary sclerosis (Jokl and Greenstein, 1944), congenital aneurysms (Gore *et al.*, 1959), and primary dissecting aneurysms of the coronary vessels in young adults (Whitehead and Dunnill, 1969), could all have their origin in the lesions described in this report. In most of these reported cases, it is difficult to trace any direct connection with anomalies of the antenatal and postnatal period, since details on these points are often scarce, not available, or not even considered. This is not entirely surprising, but in any future studies of coronary vessels in infants and children, it would be useful to ascertain as much information as possible regarding the antenatal and postnantal periods of development.

Finally, while it is clear that the lesions of the coronary artery can heal, it is equally likely that once damaged no vessel will remain perfectly normal, and it is tempting to suggest that small scars of the coronary arterial tree could predispose to the more severe plaques of later life.

I am grateful to many colleagues in the Department of Pathology and the Hamilton District Program in Laboratory Medicine for access to their material and other help, and to Sharryn Putns, Marion Leskovec, Stephanie Whittaker, and George Turcon for excellent technical assistance.

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Assessment of individual renal function in children using ^{99m}Tc-DTPA

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SUMMARY Differential renal function assessment using ^{99m}Tc–DTPA was carried out in 12 children aged between 3 weeks and 11 years who had undergone surgical procedures which allowed separate access to the urine output from each kidney. The results correlated well with those obtained by measuring individual kidney creatinine clearances. The best result was obtained using the technique of deconvolution analysis ($r = 0 \cdot 98$; $P<0 \cdot 001$). We conclude that the method is accurate and recommend its use in the management and follow-up of patients with asymmetric renal disease.

The need for a reliable noninvasive method for studying individual kidney function in children is apparent. The damage incurred by the kidneys in diseases such as vesicoureteric reflux and obstructive uropathy is seldom symmetrical, and the selection of optimal treatment and follow-up requires quantitative information about the functional status of each kidney as well as knowledge of the total renal function. An example of the type of case in which such information would be useful is that of a child with bilateral reflux nephropathy who has poor function of one kidney on intravenous urography. A decision has to be made as to whether ureteric reimplantation or nephrectomy should be carried out. It would obviously be advantageous if the relative function of the affected kidney could accurately be assessed.

Radiographic contrast techniques give valuable information about the anatomical structure of the kidneys and collecting systems. However, they provide only qualitative information on differential renal function. Bilateral ureteric cannulation for the measurement of individual kidney clearances carries the risk of introducing infection and requires general anaesthesia, and is therefore not suitable for routine use.

Attempts have been made for some time to assess individual renal function by noninvasive radioisotope techniques (Johnston and Irving, 1967; Kathel, 1971), and more recently methods using technetium-labelled stannous diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) have been described (Pieretti *et al.*, 1974; Nielsen *et al.*, 1977). The use of deconvolution analysis to quantify the renogram and the potential advantages of this method in radioisotopic assessment of renal function have been described by Kenny *et al.* (1975) and Diffey *et al.* (1976).

A method for quantitating individual renal function using ^{99m}Tc-DTPA has recently been described by Piepsz *et al.* (1977), but nonradioisotopic measurements of individual renal function were not carried out and it is therefore difficult to judge the accuracy of the technique.

The purpose of this study was to determine the accuracy of individual renal function measurements in children using ^{99m}Tc-DTPA.

Methods and materials

The 12 children studied were aged between 3 weeks and 11 years (Table 1). Informed parental consent was obtained in each case. All had undergone surgical procedures which allowed separate access to the urine output from each of their kidneys—that is, they had ureterostomies or indwelling ureteric splints. Renal function assessments were carried out at least 6 days after surgery.

Urine was collected from both kidneys simultaneously for a period of not less than 6 hours, and plasma creatinine was estimated on a blood sample taken at the time of the urine collection. All creatinine estimations were done using the auto-

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Table 1 *Results of individual kidney function assessment in 12 children*

Case	*Age*	*Diagnosis*	*% creatinine clearance*		*% uptake*							
					1–3 min		*2–4 min*		*13–15 min*		*Deconvolution*	
			Left	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
1	6½ years	Prune-belly syndrome	7	93	12	88	13	87	3	97	13	87
2	10½ years	Bilateral reflux	21	79	20	80	21	79	10	90	25	75
3	17 months	Bilateral reflux	56	44	53	47	54	46	47	53	55	45
4	2¼ years	Bilateral reflux	33	67	26	74	23	77	18	82	24	76
5	14 months	Bilateral reflux	83	17	66	34	69	31	44	56	76	24
6	6½ years	R. renal agenesis	100	0	93	7	96	4	97	3	100	0
7	19 months	Bilateral reflux	40	60	44	56	44	56	42	58	48	52
8	7 months	Bilateral reflux	55	45	51	49	50	50	46	54	51	49
9	8 months	L. pelviureteric junction obstruction	38	62	32	68	32	68	56	44	38	62
10	3 weeks	Bilateral hydronephrosis	23	77	19	81	22	78	29	71	24	76
11	3 weeks	Bilateral hydronephrosis	25	75	27	73	26	74	23	77	24	76
12	3 weeks	Bilateral hydronephrosis	37	63	26	74	27	73	26	74	43	57

analyser (6–60 Technicon). To establish the stability of the patient's renal status, two plasma creatinine estimations a day apart were performed. Individual kidney creatinine clearances were derived using the standard formula clearance = U.V/P (where U = concentration of creatinine in urine, V= volume of urine collected per minute, P= plasma creatinine concentration). The contribution of the left kidney was expressed as a percentage of the sum of the creatinine clearances of the two kidneys.

No limitations on food and drink were imposed during the estimation of creatinine clearance or before scanning, and none of the patients was receiving intravenous fluids. Scans were performed within 24 hours of creatinine clearance estimations. All the children were recumbent for at least one hour before scanning. Premedication was not routinely given beforehand, but some children required a small dose of diazepam immediately before injection of the radiopharmaceutical. To allay anxiety the parents were asked to be present during the test.

An intravenous dose of 3·7 megabecquerels (100 μCi) per kg of ^{99m}Tc-DTPA (supplied by the Australian Atomic Energy Commission) was injected as a bolus. The children lay on a foam rubber pad placed directly on the gamma camera head (Nuclear Chicago Pho-Gamma III HP Camera with low energy, high sensitivity parallel hole collimator). Data were recorded by a computer (DEC Gamma—11 system) at the rate of one frame per 5 seconds for a total of 200 frames.

Analogue scans were recorded on Polaroid and 70 mm films for one minute after the injection (one exposure every 5 seconds), followed by renal scan image (taken at a preset count of 300 000). For computer processing, regions of interest were drawn manually as close as possible to the renal outlines using a 'joystick'. In each subnephric area a background region of interest was chosen, care being taken to avoid the course of the ureters and large vessels. Another region was selected over the heart in order to generate the blood activity (heart) curve (Figs 1 and 2).

Counts for each kidney were corrected for background after the background area was normalised to the area of the ipsilateral kidney. The 120-second net counts for each kidney were integrated over the time intervals 1–3 minutes, 2–4 minutes, and 13–15 minutes. Background corrected time activity curves were displayed (Fig. 3).

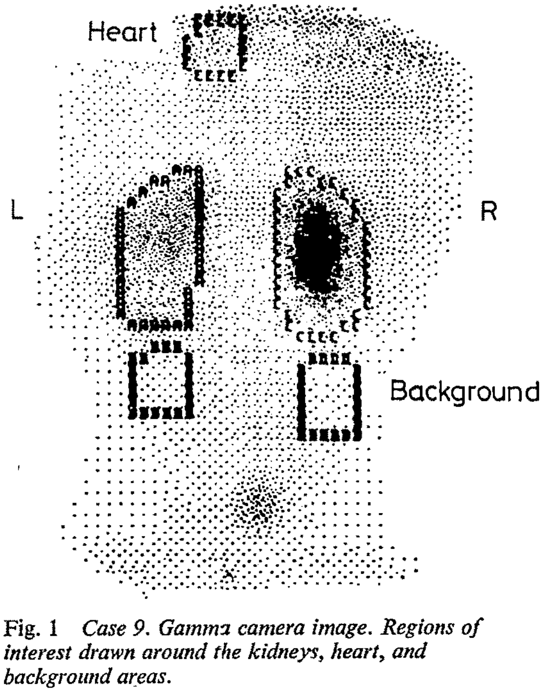

Fig. 1 *Case 9. Gamma camera image. Regions of interest drawn around the kidneys, heart, and background areas.*

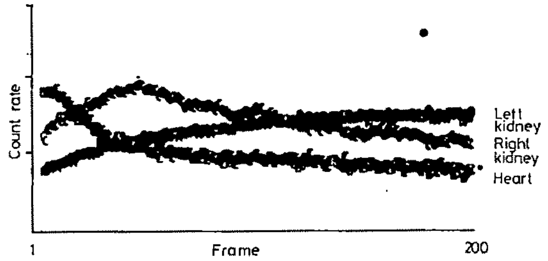

Fig. 2 *Case 9. Renograms and heart curve. Right kidney curve normal. Left kidney curve shows impaired renal function.*

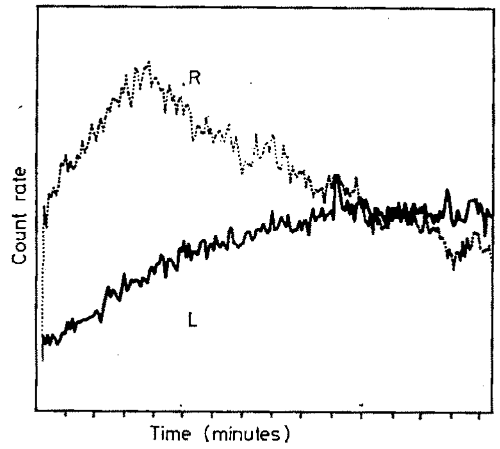

Fig. 3 *Case 9. Renograms after background subtraction. Right (R) kidney curve normal. Left (L) kidney curve shows impaired renal function.*

The percentage uptake of radioactivity for the left kidney was calculated by dividing the net counts for that kidney by the sum of the net counts from both kidneys—that is L/(L + R) × 100. The results for the three time intervals were compared with the percentage contribution of the left kidney to the total creatinine clearance (Figs 5a, 5b, 5c).

Deconvolution analysis with data bounding (Diffey and Corfield, 1975; Valentinuzzi and Montaldo Volachec, 1975) was used to plot the retention function for each of the kidneys. The retention function is the form that the renogram would take if a bolus of ^{99m}Tc-DTPA could be injected directly into the renal artery (Fig. 4). The amplitudes of the retention function curves were used to calculate the relative uptake of radioactivity by the left kidney as compared with the total, and the results compared with those obtained from creatinine clearances (Fig. 5d).

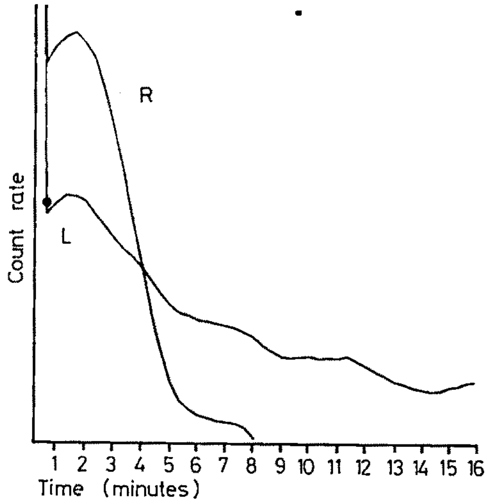

Fig. 4 *Case 9. Retention function curves derived from deconvolution analysis with data bounding. Right (R) kidney curve normal. Left (L) kidney curve shows impaired renal function.*

Correlation coefficients were derived by comparing the results obtained from scanning with those obtained from creatinine clearance estimations (Fig. 5).

95% confidence limits were determined for the results obtained from scanning methods at 1–3 minutes, 2–4 minutes, and by deconvolution analysis. Two points were chosen for determination of confidence limits—namely, where the left kidney contribution to the total renal function was 10 and 90% (Table 2).

Results

The data are presented in Table 1. The contribution of the left kidney to the total creatinine clearance,

Table 2 *Accuracy of scanning methods for predicting individual kidney function at 10 and 90% of overall renal function*

Left kidney % uptake from scans	*Prediction for % clearance of left kidney with 95% confidence limits**
1–3 min	
10	10·8 ± 6·1
90	99·9 ± 11·0
2–4 min	
10	11·0 ± 6·2
90	97·4 ± 9·1
Deconvolution	
10	8·2 ± 5·9
90	91·9 ± 7·5

*Regression analysis.

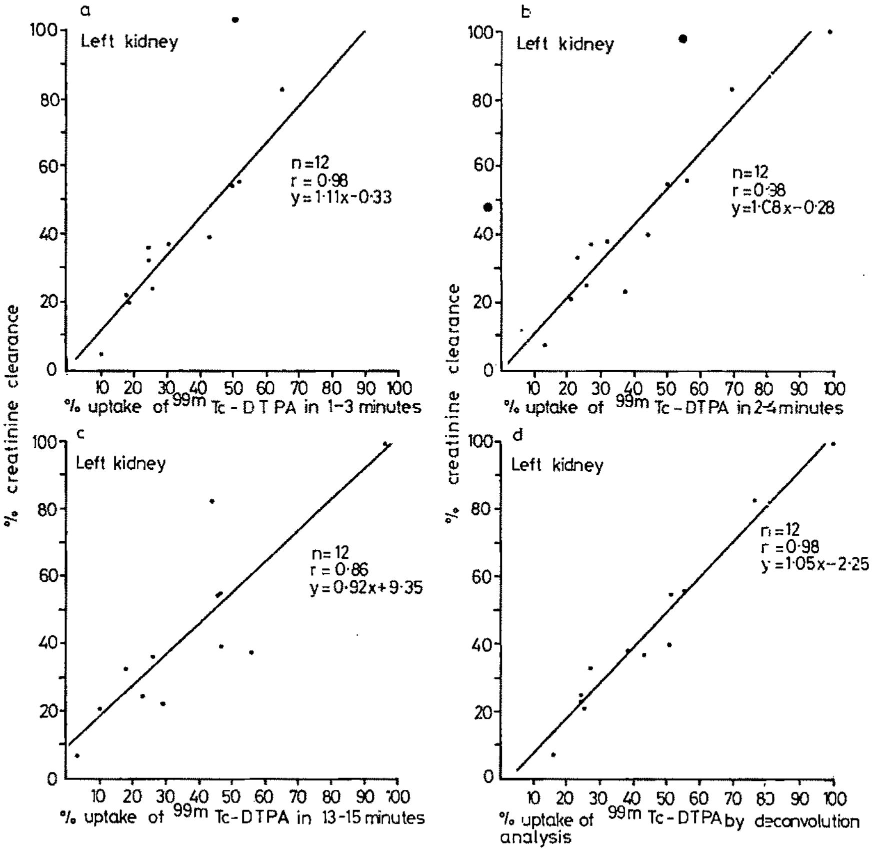

Fig. 5 *Left kidney. Percentage of total creatinine clearance v. percentage of total renal uptake of ^{99m}Tc-DTPA (a) in 1–3 min, (b) in 2–4 min, (c) in 13–15 min, (d) by deconvolution analysis.*

when compared with the results obtained using radioisotopic techniques, showed a high degree of correlation (r= 0·98) with the 1–3 minute and 2–4 minute kidney uptake ratios and with the deconvolution analysis technique. A lower correlation (r= 0·86) was found at the 13–15 minute interval. All were significant ($P<0·001$).

The mean disparity between the scan results and those obtained from creatinine clearances was 6% for the 1–3 minute, 5% for the 2–4 minute, and 11% for the 13–15 minute uptake ratios, and 4% for the deconvolution analysis method.

The calculated predictions for left renal function from the data, using regression analysis, are presented in Table 2.

Discussion

The required characteristics of any substance for the measurement of glomerular filtration rate (GFR) are: (1) It must be preferentially excreted by the kidney. (2) It must be freely filtered through the glomerular basement membrane. (3) It must be physiologically inert. (4) It must not be reabsorbed or secreted by the renal tubules.

The classical substance fulfilling the above criteria is inulin (Materson, 1971). However, determination of inulin concentration is difficult and the technique does not lend itself to routine hospital use. Inulin is not readily labelled by available gamma-emitting radionuclides of suitable energy, radiation, or half-life. One of the newly developed substances with physiological characteristics closely resembling those of inulin is DTPA (Reba *et al.*, 1974; Barbour *et al.*, 1976). This chelating agent can be readily labelled with various radionuclides, including ^{99m}Tc. The resulting complex is suitable for radioisotopic determination of GFR (Hauser *et al.*, 1970; Chevru *et al.*, 1974).

^{99m}Tc has ideal physical characteristics for application in nuclear medicine. It has a short half-life (6 hours) and suitable radiation characteristics (140 keV photons in 90% abundance and no beta radiation). The 140 keV photon has adequate tissue penetration and is efficiently measured by the current generation of gamma cameras. Its low radiation dose permits repeated examinations in children (Chevru *et al.*, 1974; Kirchner *et al.*, 1975).

The ^{99m}Tc-DTPA complex, after intravenous injection, equilibrates rapidly throughout its extracellular distribution space. It is cleared through the glomeruli without appreciable tubular secretion or reabsorption and only 5% is excreted in the faeces. More than 98% of the radioactivity remains in the chelated form and only 5–10% of the serum radioactivity at one hour after injection is associated with serum proteins (Hauser *et al.*, 1970; Arnold *et al.*, 1975).

This study demonstrated that individual renal function in children can accurately be assessed using ^{99m}Tc-DTPA and external monitoring with computerised quantitation. The deconvolution analysis method gave the best results, but the 1–3 minute and 2–4 minute kidney uptake ratios were also satisfactory.

Statistical testing of the accuracy of these methods at the extremes of renal function—that is 10 and 90% function in one kidney, gave results quite adequate for clinical use (Table 2). The best methods for measuring GFR have an accuracy of ± 3–6% (Materson, 1971). 10 and 90% levels of individual renal function were chosen because it is at these levels of relative function that decisions regarding nephrectomy are most often made.

On computer analysis of the gamma camera data, it is essential to draw the regions of interest as closely as possible around the renal outlines; this is particularly important for the relative uptake method. Inclusion of extrarenal areas tends to reduce the average count in each matrix element. For the deconvolution analysis method the selection of a region of interest close to the kidney outline is not as critical, provided it includes all functioning renal parenchyma.

All the children were recumbent for at least one hour before and during the time of scanning. This was felt to be important as changes in posture may lead to alterations in urodynamics and haemodynamics. The positioning of the child on top of the collimator made venepunctures easier and was found to be less frightening for the child than prone with the gamma camera head suspended above.

It was found that background regions of interest were most representative in the subnephric regions. Other sites such as areas lateral to the kidneys were found to be technically unsatisfactory in smaller children with hydronephrosis. In one child (Case 6, Table 1) with unilateral renal agenesis, the counts obtained in the subnephric area virtually equalled the counts obtained from the site where the kidney would normally have been situated.

Apart from its use in determination of individual renal function, scanning with ^{99m}Tc-DTPA may also be helpful in the demonstration of anatomical abnormalities of the kidneys and collecting systems, and in the diagnosis of urinary obstruction. Obstruction to urine outflow can be inferred from the shape of the renogram and from the retention function curve after deconvolution analysis (left kidney; Figs 3 and 4). Retention of radioactive material due to obstruction is best assessed by the net cumulative count at the 13–15 minute time interval (for example, Case 8, Table 1).

In summary, we have shown that assessment of individual renal function with ^{99m}Tc-DTPA in children is accurate. It carries less risk and is no more disturbing to the child than a comparable radiological investigation. It can be done in any hospital with a modern nuclear medicine department. We believe that the use of this technique will prove to be important in the management and follow-up of patients with asymmetric renal diseases and also in the understanding of the evolution of these disorders.

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TSH and PRL response to thyrotrophin-releasing hormone in children with chronic renal failure undergoing haemodialysis

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SUMMARY Eight children (aged between 8½ and 15½ years) with chronic renal failure receiving intermittent haemodialysis, and 2 children with renal transplants were studied. The response of TSH and prolactin (PRL), and basal T4 and T3 values was measured. Basal TSH was normal, and rose only slightly after TRH stimulation. Plasma T4 and T3 were below normal levels in 6 children. Mean basal PRL was raised and could not be stimulated by TRH. This study demonstrates the involvement of the hypothalamus and pituitary in chronic renal disease. The cause of the abnormal secretion of TSH and PRL in chronic renal failure is discussed in the light of clinical importance.

Pituitary, thyroid, and gonadal hormones are important in the growth, skeletal, and sexual maturation of children. Endocrine abnormalities have been reported in patients with chronic renal failure (Feldman and Singer, 1975), in whom synthesis, secretion, and degradation of the affected hormones and their activity on target organs are impaired. In uraemic children, endocrine abnormalities have been observed by Czernichow *et al.* (1976) and Ijaiya *et al.* (1978), but information in this age group is scanty.

The present study was undertaken to assess hypothalamic and pituitary functions in children with chronic renal disease.

Patients and methods

Eight children with chronic renal failure (CRF) undergoing haemodialysis for 1 to 86 months, and 2 children who had had successful renal transplants 25 and 44 months earlier were investigated. Clinical details are shown in Table 1. Haemodialysis was generally performed for 6 hours 3-times a week.

No child showed galactorrhoea or gynaecomastia and no thyroid disease had been diagnosed. The aims of the study were explained to the patients and their parents and their informed consent was obtained. 22 (12 girls and 10 boys) healthy children, aged between 8 and 15 years, in hospital because of their short stature served as a control group. Five of these children have achieved almost complete sexual maturation, the rest were prepubertal. They were in

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Table 1 *Clinical data of 8 children with chronic renal failure and 2 children with renal transplants*

Case	*Sex*	*Age (years)*	*Pubertal status**	*Bone age† (years)*	*Height (cm)*	*Diagnosis*	*Haemodialysis treatment (months)*	*Other treatment*
1	F	15·6	Stage 3	15	144	Chronic pyelonephritis	48	—
2	M	8·5	Stage 1	5	122	Haemolytic uraemic syndrome	10	—
3	M	9·0	Stage 1	7	124	Haemolytic uraemic syndrome	1	α-Methyldopa, reserpine, dihydrallazine
4	M	12·6	Stage 1	12	132	Oxalosis	12	Frusemide
5	F	15·2	Stage 3	15	147	Renal hypoplasia	86	—
6	F	12·8	Stage 1	11½	147	Polycystic kidney	22	—
7	F	15·1	Stage 2	13½	150	Chronic pyelonephritis	4	—
8	F	11·0	Stage 1	8	120	Glomerulonephritis	54	—
9	M	15·5	Stage 1	10	138	Megacystis-megaureter-syndrome	—	Renal transplant
10	M	14·2	Stage 1	7	134	Glomerulonephritis	—	Renal transplant

*Pubertal status rated according to Tanner and Whitehouse (1976), †bone age estimated according to Greulich and Pyle (1959).

good health and endocrine studies showed no abnormality.

Synthetic TRH (Relefact TRH, Hoechst AG, Frankfurt) was administered intravenously at a dose of 200 µg dissolved in 2 ml saline. All children were fasted overnight and remained in bed before and during the test. The test was performed at least 18 hours after haemodialysis. Blood samples were withdrawn through an indwelling cannula in an arm vein at 0, 15, 30, 45, 60, 90, and 120 minutes after TRH injection. Heparinised blood was immediately centrifuged at 4°C, and the plasma stored at −20°C until assayed for TSH, PRL, T4, and T3. Plasma TSH was determined by a double antibody radioimmunoassay (Utiger, 1965) (Amersham Buckler, Düsseldorf, Germany) (normal value, 0–7 µU/ml); plasma PRL by the double antibody method of Reuter *et al.* (1976) (Union Carbide, Sleoros, Belgium) (normal 6–10 ng/ml); plasma T4 by a competitive protein-binding radioassay (Res-O-Mat T4, Byck-Mallinchrodt Co, Dietzenbach, Germany) (normal 4·5–11·4 µg/100 ml), and T3 by radioimmunoassay (T3 RIA-KIT, Serono, Freiburg, Germany) (normal 0·6–1·7 ng/ml).

Statistical evaluations were by the Wilcoxon, Mann and Whitney U test for unpaired groups.

Results

Mean plasma concentration and SDs for basal TSH, PRL, T4, and T3 in controls and in children with CRF are shown in Table 2 which also shows the peak levels after TRH stimulation. The range of values and the results in the children with transplants are shown in Figs 1 and 2. No significant difference in basal levels of TSH, T4, or T3 was found. However, 6 of the 8 children with CRF had T3 or T4 levels below the normal range; PRL basal levels were significantly higher in the children with CRF failure. Basal levels were within the normal range in the children with transplants. After TRH stimulation, TSH rose in both groups with a peak response >8·0 µU/ml. In 5 cases TSH values had not fallen to basal levels 90 minutes after TRH injection. PRL levels after TRH stimulation rose in the control children, but were not significantly different from basal levels in children with CRF. Case 3, who was receiving medication for acute hypertension (Table 1) and who had been on dialysis for only one month, had a normal basal PRL level (4·8 ng/ml) with only a slight rise after TRH. Sex, puberty, or duration of haemodialysis had no influence on the raised basal

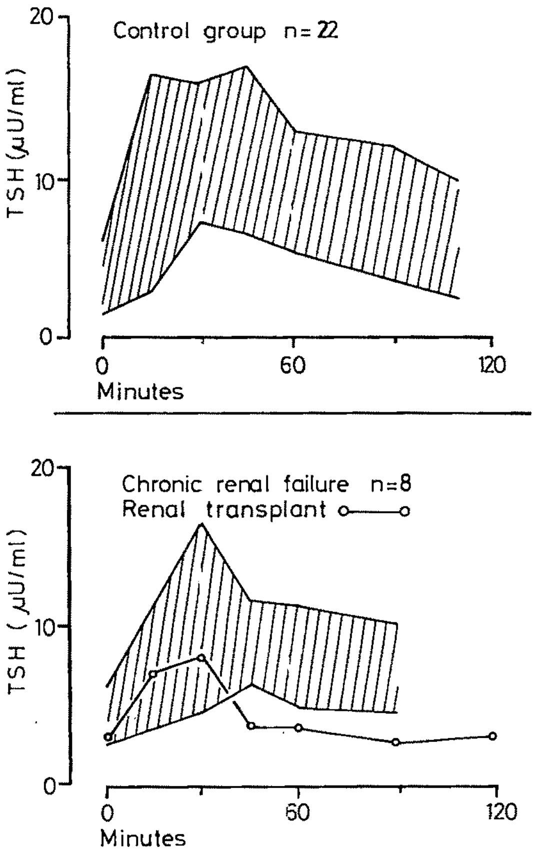

Fig. 1 *Serum TSH concentrations after IV TRH in 8 children with chronic renal failure and one child with transplant, compared with 22 healthy children. Range is shown as mean values ± SD.*

Table 2 *Mean plasma concentration (and SD) for basal serum TSH, prolactin, T4, and T3, and peak levels after TRH stimulation in controls and in children with chronic renal failure*

Group	*TSH (µU/ml)*		*PRL (ng/ml)*		*T4 (µg/100ml) basal*	*T3 (ng/ml) basal*
	Basal	*Peak*	*Basal*	*Peak*		
Controls (n = 22)	3·8 (2·3)	12·0 (4·2)	5·5* (2·9)	30·6 (11·1)	8·27 (2·23)	1·17 (0·23)
Chronic renal failure (n = 8)	4·5 (1·8)	9·8 (5·2)	17·8* (9·9)	21·4 (8·1)	5·98 (2·16)	0·59 (0·20)

* = U test 2α <0·05.

Conversion: traditional units to SI—T4: 1 µg/100 ml ≈ 12·87 nmol/l, T3: 1 ng/ml ≈ 1·536 nmol/l.

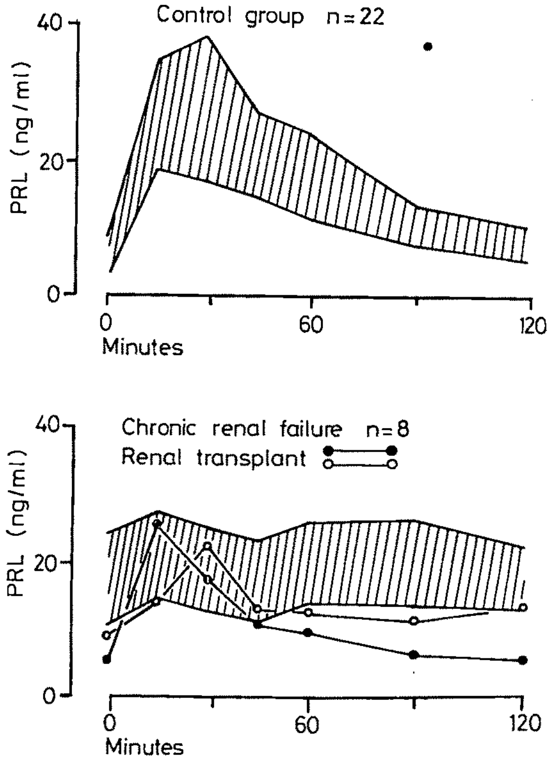

Fig. 2 *Concentration of serum PRL after IV TRH. Range is shown as mean values ± SD in 8 children with chronic renal failure and 2 children with successful renal transplants, compared with 22 healthy children.*

level of plasma PRL, or on the failure to increase PRL concentration after TRH injection in children with CRF.

Discussion

Studies of thyroid function in patients with CRF have produced conflicting results; both hyperthyroidism (Schmidt *et al.*, 1971) and hypothyroidism with low T3 and T4 levels have been reported (Ramirez *et al.*, 1972; Czernichow *et al.*, 1976; Kølendorf *et al.*, 1978). Raised plasma-free thyroxine was reported by Bailey *et al.* (1967) in dialysed patients, and after successful renal transplants these parameters returned to normal. Heparin administration during haemodialysis raises levels of free T4, but not total T4 (Schatz *et al.*, 1969).

The thyroxine-binding capacity of TBG in chronic renal failure is normal (Joasso *et al.*, 1974; Kølendorf *et al.*, 1978), whereas the binding capacity of thyroxine-binding prealbumin is low (Jaffiol *et al.*, 1970). Joasso *et al.* (1974) suggested that the change in serum T4 was due to some unidentified substance, which displaces T4 from TBG in serum of patients with renal failure. TSH, T4, and T3 are not dialysable (Bindeballe *et al.*, 1973; Silverberg *et al.*, 1973). Impairment of the peripheral conversion of T4 to T3 was also suggested (Lim *et al.*, 1977). Normal ^{131}I uptake after stimulation of thyroid with TSH in dialysed patients has been reported (Silverberg *et al.*, 1973).

Except in cystinosis, primary thyroid disease is unlikely to be responsible for the low levels of thyroid hormones (Burke *et al.*, 1978). TSH production might be expected to be stimulated by low levels of thyroid hormones, and raised basal value of serum TSH in dialysed patients has been reported (Waldhäusl *et al.*, 1971); others have found normal (Czernichow *et al.*, 1976) or low values (Silverberg *et al.*, 1973). Basal TSH was normal in our patients.

Despite low serum thyroid hormones and normal basal TSH level, exogenous TRH could not stimulate pituitary TSH release, suggesting a defect in pituitary secretion of TSH (Ramirez *et al.*, 1972; Silverberg *et al.*, 1973). The negative feedback mechanism seems, however, to be intact, for high dosages of T3 lowered TSH (Czernichow *et al.*, 1976). The cause of the pituitary abnormalities in these patients is unknown; severe malnutrition or uraemic toxins may be involved (D'Angelo, 1951; Feldman and Singer, 1975).

A trial of thyroid hormone replacement in dialysed uraemic patients with low serum T4 levels and clinical symptoms of hypothyroidism gave inconsistent results (Silverberg *et al.*, 1973). Chan *et al.* (1970) reported a 10-year-old boy with CRF and clinical signs of hypothyroidism who showed an increase in height velocity after starting thyroid extract. Increased growth velocity with thyroid supplementation occurred in only 2 out of 7 patients treated by Burke *et al.* (1978). An improvement in growth and better pubertal development may be achieved with thyroid hormone replacement.

An abnormal response of PRL to TRH, with raised basal PRL which could not be stimulated after TRH injection has been reported in uraemic patients (Czernichow *et al.*, 1976; Archer, 1977; Sciarra *et al.*, 1977). Despite the increased PRL, no galactorrhoea or gynaecomastia was observed. The high prolactin may be responsible for the hypogonadism or amenorrhoea in several patients (Thorner, 1977). Whether the hyperprolactinaemia in the uraemic child affects gonadal maturation, and therefore delay in puberty, needs further clarification. The cause and clinical importance of the raised PRL are still poorly understood. High PRL levels are found in primary hypothyroidism (personal observation) often combined with the triad galactorrhoea, precocious puberty, and hypothyroidism (van Wyk and Grumbach, 1960). None of our patients exhibits clinical signs of hypothyroidism. The abnormal TSH response to TRH would even suggest a secondary hypothyroidism. In our patient receiving medication for acute hypertension PRL secretion was normal. This is despite the fact that several drugs—such as reserpine and α-methyldopa—have been found to increase serum PRL levels (Archer, 1977; Thorner, 1977).

The source of high PRL values in uraemic patients is still unknown. A loss of renal degradation cannot be the only cause, several other peptide hormones are not raised. Cowden *et al.* (1978) demonstrated a progressive rise in PRL concentrations as renal function deteriorates, and a return to normal after successful renal transplants. PRL is supposed to have a fundamental osmoregulatory role in many species of fish and amphibians (Lam, 1972). Its possible role as an osmoregulator in man remains controversial. The role of the hypothalamus and pituitary in the abnormal secretion of PRL is obscure. Since increased PRL secretion is due to a decrease in hypothalamic prolactin-inhibiting factor or an increase in prolactin-releasing factor (L'Hermite *et al.*, 1974), a dysfunction of the hypothalamus may result in decreased prolactin-inhibiting factor or increased prolactin-releasing factor biosynthesis or secretion.

This study has demonstrated the involvement of the hypothalamus and pituitary in children with CRF. Levels of T3 and T4 tend to be low and this is due to inadequate TSH production. PRL is high, but the pituitary reserve is limited so it does not rise further after TRH stimulation. The renal cause of the hypothalamic-pituitary dysfunction remains poorly understood.

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Persistent pulmonary hypertension and abnormal prostaglandin E levels in preterm infants after maternal treatment with naproxen

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SUMMARY Twins and a singleton were born at 30 weeks' gestation although naproxen (d-2 (6'methoxy-2-naphthyl) propionic acid) had been given to the mothers in an attempt to delay parturition. Inhibition of prostaglandin synthesis was shown by very low plasma concentrations of prostaglandin E and the ductus arteriosus remained closed despite signs of pulmonary hypertension with severe hypoxaemia. Abnormalities in blood clotting, renal function, and bilirubin metabolism were also found and one infant died. Further studies of the benefits and risks of the inhibition of prostaglandin synthesis are required before this treatment of preterm labour is accepted.

Indomethacin and salicylates are prostaglandin synthetase inhibitors (PGSI), which suppress uterine activity in animals and humans (Wigvist *et al.*, 1975). Some workers have used PGSI to treat women after the onset of preterm labour (Zuckerman *et al.*, 1974), but experiments in lambs (Heymann and Rudolph, 1976; Levin *et al.*, 1979) show that these drugs cross the placenta and cause great changes in the fetal circulation with closure of the ductus arteriosus and an increase in pulmonary arterial pressure. Postnatal persistent pulmonary hypertension has been described after maternal treatment with indomethacin and salicylates (Manchester *et al.*, 1976; Csaba *et al.*, 1978; Levin *et al.*, 1978). We report 3 premature infants with this syndrome who were born to mothers who had been given naproxen (d-2 (6'methoxy-2-naphthyl) propionic acid) which is another potent PGSI.

Case 1

A girl weighing 1·28 kg was born at 30 weeks' gestation to a 28-year-old mother. There had been recurrent vaginal bleeding throughout pregnancy and at 28 weeks uterine contractions became frequent. Naproxen 250 mg was given orally 8-hourly for 6 days and contractions became less frequent but 48 hours after stopping naproxen spontaneous labour recurred. The baby was delivered by caesarean section because of breech presentation. The Apgar score was 2 and the baby was resuscitated with oxygen and positive pressure ventilation, but cyanosis persisted and tachypnoea developed. Artificial ventilation was continued and at 40 minutes while breathing 50% oxygen arterial pH was 7·04, Pa_{O_2} 3·0 kPa (23 mmHg), and Pa_{CO_2} 7·9 kPa (59 mmHg). Breath sounds were normal and no heart murmurs were heard. The haematocrit was 52% and blood glucose concentration normal. Parenchymal and vascular markings and the heart size were normal on chest *x*-ray. The inspired oxygen concentration was raised to 100% and ventilation pressure to 30 cmH_2O with 4 cmH_2O end-expiratory pressure. Fig. 1 shows that despite these changes, the Pa_{O_2} could not be raised above 6·7 kPa (50 mmHg) until 6 hours after birth. At 10 hours, right radial and umbilical artery blood-gas tensions were identical (Fig. 1). She required assisted ventilation until 63 hours of age and additional oxygen until the fifth day. There was no evidence of pneumonia, hyaline membrane disease, or aspiration. Urine was not passed until 24 hours and plasma bilirubin rose to 252 μmol/l (14·7 mg/100 ml). Bleeding time was prolonged but platelet count and clotting studies were within normal limits. At discharge, age 61 days, she weighed 2·2 kg and examination was normal.

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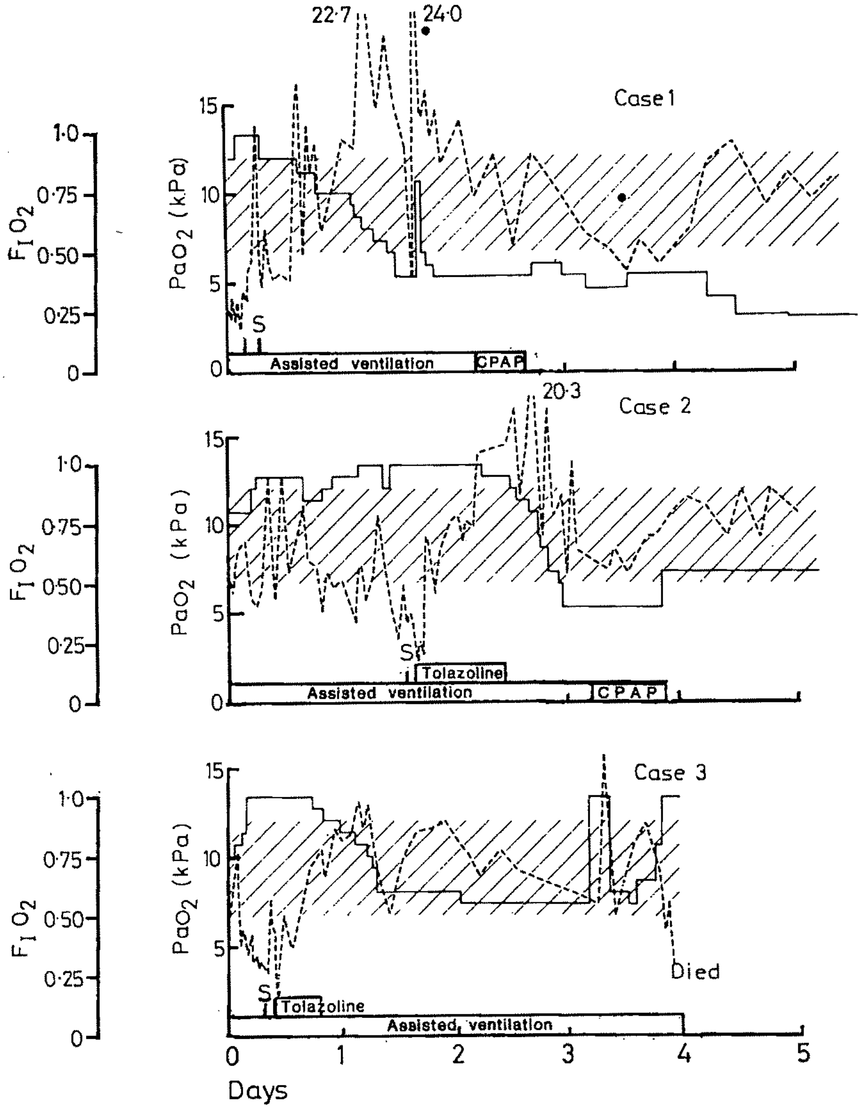

Fig. 1 *Inspired oxygen concentration (F_{IO_2})—continuous line, and arterial oxygen tension (Pao_2)—dotted line. Hatched area shows normal range of Pao_2. Effect of tolazoline hydrochloride is shown in Cases 2 and 3. S = identical gas tensions in umbilical and right radial arterial blood and blood samples taken for prostaglandin assay. Conversion: SI to traditional units* 1 kPa ≈ 7·5 mmHg

Cases 2 and 3

Twin girls were delivered by caesarean section at 30 weeks' gestation to a 20-year-old mother after a pregnancy complicated by vaginal bleeding and preterm labour. 30 hours before delivery naproxen 250 mg 8 hourly had been begun. A total of 1 g was given, the last dose 5 hours before delivery.

The first twin weighed 1·18 kg. The Apgar score was 1 and positive pressure ventilation was given immediately. At 30 minutes while breathing 80% oxygen arterial pH was 7·05, Pao_2 6·7 kPa (51 mmHg), and $Paco_2$ 10·8 kPa (81 mmHg). The lung fields were clear and the heart size normal on chest *x*-ray. Haematocrit and blood glucose concentration were normal and the lecithin/sphingomyelin ratio (L/S) was 2·0 in the pharyngeal aspirate. The hypercarbia was rapidly corrected by artificial ventilation but Pao_2 remained low despite pressures up to 35 cmH_2O and 100% oxygen. Simultaneous right radial and umbilical blood-gas tensions taken when the baby was unresponsive were identical at 40 hours (Fig. 1). Tolazoline hydrochloride (2 mg/kg, IV) produced an immediate improvement in oxygenation (Fig. 1) which was maintained by an infusion (2 mg/kg per hour) for 20 hours. Assisted ventilation was necessary for 5 days after which chronic lung disease with oxygen dependency persisted for 12 weeks. During the first 2 days plasma bilirubin rose to 225 µmol/l (13·2 mg/100 ml) and bleeding time, prothrombin time, and partial thromboplastin time were prolonged. Urine volume was markedly reduced until the third day.

The second twin was delivered 2 minutes later and weighed 1·26 kg. The Apgar score was 1 and severe hypoxaemia rapidly developed. Treatment and investigations were similar to those in the first twin. The L/S ratio was 3·1, and within the first 24 hours the bilirubin rose to 230 µmol/l (13·5 mg/100 ml). Bleeding from the umbilical stump and heel punctures was prolonged and the clotting studies were abnormal. At 3 hours an intracranial haemorrhage was suspected. At 10 hours tolazoline hydrochloride (2 mg/kg, IV) rapidly improved oxygenation (Fig. 1) and during the next 60 hours ventilatory assistance was gradually withdrawn. However, at 80 hours she suddenly became apnoeic with a distended abdomen and poor peripheral perfusion. Cardiac arrest occurred and resuscitation was unsuccessful. Necropsy showed a subarachnoid haemorrhage and blood in both ventricles. Multiple gastric ulcers were present and there was blood throughout the intestine. The ductus arteriosus was short and constricted and hyaline membranes were not seen in sections of the lungs.

Assay of plasma prostaglandins. The plasma concentrations of prostaglandins E and F (PGE and PGF), and 13, 14-dihydro-15-keto-PGF (PGFM) (the major circulating metabolite of PGF), were measured by methods described previously and in Fig. 2 the values at 10, 40, and 10 hours age are compared with the levels found in preterm infants of the same age who were not ill (Mitchell *et al.*, 1978).

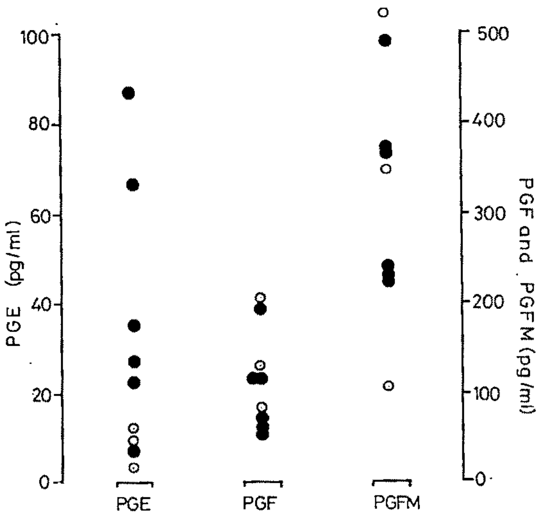

Fig. 2 *Plasma concentration of PGE, PGF, and PGFM (pg/ml) (open circles), compared with concentrations in preterm infants without cardiopulmonary disease (closed circles).*

Discussion

Persistent pulmonary hypertension presents during the first hours of life with arterial oxygen desaturation in the absence of parenchymal pulmonary disease or cardiac malformation. The mechanisms responsible are not known but an altered structure or abnormal response of the smooth muscle of the pulmonary arterioles has been suggested (Levin *et al.*, 1978). The condition has been associated with birth asphyxia, hypoglycaemia, hypocalcaemia, and hyperviscosity. The 2 infants who survived (Cases 1 and 2) were not hypoxaemic at birth. Umbilical cord vein Po_2 was 4·1 and 2·9 kPa (31 and 22 mmHg). In Case 3 the umbilical cord was so friable that blood could not be obtained. Undoubtedly hypoxaemia after birth contributed to maintaining the high pulmonary vascular resistance. Cassin *et al.* (1978) showed that this effect of hypoxia is potentiated by indomethacin and meclofenamate (another PGSI). In their experiments with goats the response to indomethacin was more pronounced in the premature than mature newborn. They also reported than an infusion of PGE abolishes the response to hypoxia and can reverse the effect of the PGSI.

Constriction of the ductus arteriosus and pulmonary arterial hypertension after maternal indomethacin administration in fetal lambs has been reported by Levin *et al.* (1979). This effect was also reversed promptly but temporarily by an infusion of PGE. In the 3 infants described here the identical gas tensions in blood drawn simultaneously from both sides of the ductus arteriosus (Fig. 1) and the absence of a ductal flow murmur suggests that the ductus arteriosus had constricted. The very low concentrations of prostaglandin E in all 3 babies (Fig. 2) supports the view that this prostaglandin plays an important role in maintaining relaxation of the ductus arteriosus *in utero* and that constriction may follow inhibition of prostaglandin synthesis.

The association between pulmonary hypertension and inhibition of prostaglandin synthesis in humans was first suggested by Manchester *et al.* (1976) who described 2 cases after treatment with indomethacin, and the report by Zuckerman *et al.* (1974) included 5 infants who died within 48 hours. Csaba *et al.* (1978) reported 2 deaths in 5 infants after indomethacin and Levin *et al.* (1978) reported 2 deaths, one each after salicylate and indomethacin treatment, in which they found an increase in pulmonary arterial smooth muscle and a decrease in the number of pulmonary vessels. This report is the first to implicate naproxen in a similar role.

When the severe hypoxaemia of the twins (Cases 2 and 3) was refractory to other treatment we gave tolazoline hydrochloride which caused a large rise in Pao_2 (Fig. 1). There was a pronounced skin flush and fall in systolic blood pressure from 58 to 35 mmHg and 69 to 39 mmHg which was restored immediately by infusing albumin and blood. Tolazoline is a potent pulmonary and systemic vasodilator and blood pressure must be continuously monitored to detect severe hypotension. The gastric ulceration and bleeding found at necropsy (Case 3) was probably due to the histaminic action of tolazoline on gastric secretion. It is less certain whether the cerebral bleeding preceded the infusion of tolazoline or not.

The role of naproxen in the aetiology of early hyperbilirubinaemia, the abnormalities in blood clotting, and the impairment of renal function remain to be defined.

There is no universally effective and safe way of delaying preterm labour, and only when details of all the effects of PGSI are known will it be possible to decide whether there is any benefit to the fetus from this form of treatment. At present the possible hazards outweigh the theoretical advantage taking into account the improved prognosis for premature infants with current management.

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Maturation of caffeine elimination in infancy

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SUMMARY The developmental changes in caffeine elimination were studied in 7 infants aged between 2½ weeks and 6 months. Adult plasma clearance rate of caffeine was achieved at 3 to 4½ months of age. Plasma half-life and elimination rate reached adult levels after 3 to 4½ months and seemed to exceed adult capacity thereafter. No significant changes in apparent volume of distribution were noted. Our data provide some indication of the age in infancy when the low rates of caffeine elimination in the neonate increase to the adult rate.

Caffeine (1, 3, 7, trimethylxanthine) is a central nervous system stimulant with many pharmacological activities. It is an ubiquitous compound found in many beverages, food, and medicines. Substantial exposure of the developing human organism to this compound occurs via placental transfer (Parsons *et al.*, 1976; Bory *et al.*, 1979) postnatally via breast milk (Horning, 1977) or intentionally in the treatment of neonatal apnoea (Aranda *et al.*, 1977a). The elimination of this drug in the human neonate is exceedingly slow, far more so than is the case with other drugs (Aranda *et al.*, 1977b, 1979). The plasma half-life and clearance in the premature neonate ranges from 40 to 230 hours (mean = 100) and 2·5 to 16·8 ml/kg per h (mean = 8·9), respectively. This implies that the breast-fed newborn and young infant with a significant daily intake of caffeine via maternal breast milk could potentially accumulate caffeine in the body. However, beyond the neonatal period, there are no data on the elimination of caffeine, and the present study therefore attempts to define how caffeine elimination changes in early infancy. The investigative use of caffeine for the prevention of 'cot death' has afforded the opportunity to perform these studies.

Materials and methods

A total of 10 doses of caffeine citrate, 8 as single IV infusions and 2 as single oral doses, were given to 7 infants whose ages ranged from 2½ weeks to 6 months. Five infants were admitted for investigation of 'near-miss' sudden infant death syndrome. An additional 2 sick infants with severe apnoea were also included. One 3-month-old infant had complex congenital heart disease, congestive heart failure, and apnoea, and was respirator dependent. One 6-month-old infant had persistent apnoea with Arnold-Chiari malformation. One infant with 'near-miss' sudden infant death syndrome was studied at ages 2½, 5, and 10 weeks. Another infant was also studied sequentially at ages 4½ and 5 months. Informed consent was obtained from the parents. This study protocol was approved by the Scientific Review Committee and the Ethics Committee of the Montreal Children's Hospital.

After the IV or oral administration of caffeine citrate (10 mg/kg of caffeine base), multiple capillary blood samples were obtained at varying intervals from 30 minutes to 72 hours. Using a plasma volume of 10 μl, caffeine was measured by radioimmunoassay as described by Cook *et al.* (1976). Metabolite cross-reactivity is negligible as previously determined at this laboratory.

Data were analysed using a one-compartment model. This analysis has been shown to be applicable in the pharmacokinetic disposition of caffeine in the newborn (Aranda *et al*, 1979), and of theophylline in the newborn (Aranda *et al.*, 1976) and young infant (Loughnan *et al.*, 1976). The plasma concentrations of caffeine were plotted semilogarithmically and the slope of the curve (elimination rate constant or K_{el}) was calculated with the use of log-linear least-square regression analysis. Apparent volume

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of distribution (AV_d) was calculated as dose over the plasma concentration extrapolated to time zero (C_p^o). Plasma half-life was derived from $0{\cdot}693/K_{el}$ and the clearance rate as the product of K_{el} and AV_d. In the 2 infants who received caffeine orally, analysis assumed complete bioavailability of the drug.

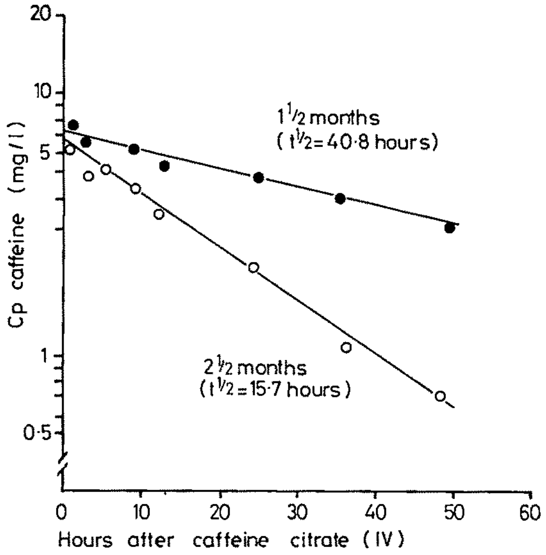

Figure *Plasma disappearance curve of intravenously administered caffeine in the same infant at ages 1½ and 2½ months. Caffeine citrate, 10 mg/kg and 5 mg/kg of active caffeine base, were infused at ages 1½ and 2½ months, respectively. Plasma disappearance curve of caffeine in this infant at an earlier age (2½ weeks) was similar to the value obtained at age 1½ months (t½ — 40·8 hours).*

Results

The Figure shows the sequential changes in the plasma disappearance curve of caffeine in a young infant with increasing postnatal age. The Table shows the pharmacokinetic profile of caffeine as a function of age. Comparative data for the newborn and adults from the same laboratory were included. There was little change in the mean AV_d over the age period studied. Plasma half-life shortened by 1–2½ months of age and attained adult t½ by between 4 and 6 months. Plasma clearance of caffeine progressively increased and achieved comparable adult capacity by 3 to 4½ months and exceeded adult capacity by 5 to 6 months of age. Change in clearance was mainly a function of an increased elimination rate constant. There was a wide variability in the elimination rate and clearance of caffeine in the newborn and young infant. This wide variability was also observed in adults (Table).

Discussion

The observation that drugs are eliminated more slowly by neonates than by adults is no longer surprising but the magnitude and duration of the deficit in the case of caffeine exceeds expectations based on the behaviour of other drugs—such as theophylline (Aranda *et al*,. 1976), phenytoin (Loughnan *et al.*, 1977; Painter *et al.*, 1978), and phenobarbitone (Jalling, 1975; Painter *et al.*, 1978). Both phenytoin and phenobarbitone exhibit 2-to 6-fold prolongation in the plasma half-life relative to the adult (Neims *et al.*, 1976) and the adult level of elimination is achieved within the first month of postnatal life (Neims *et al.*, 1976). In contrast, the plasma half-life

Table *Developmental changes in the pharmacokinetic disposition of caffeine in young infants**

Age group	*AV_d (l/kg)*	*t½ (h)*	*K_{el} (h^{-1})*	*Clearance (ml/kg per h)*
Premature neonates (n = 12) 3–32 days	0·916 (0·475–1·280)	102·9 (40·8–231)	0·009 (0·003–0·017)	8·9 (2·5–16·8)
Term neonates (n = 15) 0–4 days	—	80·0† (26)	—	—
Present report				
Young infants (n = 7)				
1–2½ months (n = 5‡)	0·878 (0·58–1·72)	26·3 (7·5–40·8)	0·039 (0·017–0·093)	31·5 (16·2–53·9)
3–4½ months (n = 3§)	0·813 (0·44–1·41)	14·2 (3·6–28·9)	0·094 (0·024–0·191)	104·6 (14·2–269·3)
5–6 months (n = 2≈)	1·120 (0·70–1·54)	2·6 (2·1–3·1)	0·276 (·224–0·329)	331·7 (156·8–506·7)
Adults ø				
Nonsmokers	0·610 (0·12–1·02)	6·0 (3·0–9·4)	0·130 (0·074–0·234)	94·0 (21·0–270·0)
Smokers	0·720 (0·12–0·97)	3·5 (1·5–5·9)	0·230 (0·117–0·461)	155·0 (69·0–268·0)

*Comparative data obtained from the same laboratory. Values expressed as mean and range.

†Disappearance curve drawn from 2 points: cord blood sample and a 4-day sample (Parsons *et al.*, 1976), ‡includes 3 sequential studies in one infant, §includes 1 infant with congenital heart disease and respiratory dependency, ≈includes 1 infant with Arnold-Chiari malformation on phenobarbitone and phenytoin, ø smoking accelerates caffeine elimination (Parsons and Neims, 1978).

of caffeine represents a 17-fold prolongation relative to the adult, and the adult capacity to eliminate the drug is achieved much later (3–4½ months).

One biochemical basis for this finding could be a decreased oxidative metabolism of caffeine by the newborn and young infant (Aranda *et al.*, 1974; Neims *et al.*, 1976). In adults, less than 2% of a caffeine dose is eliminated unchanged in urine, the remainder being metabolised in the liver to a series of partially demethylated xanthines and methyl uric acids (Cornish and Christman, 1957; Burg, 1975). In contrast, Horning *et al.* (1975) found that transplacentally acquired caffeine was largely excreted unchanged in comparison with its demethylated metabolites in the urine of 1- to 3-day-old neonates. This was confirmed by Aldridge *et al.* (1979), who found that unchanged caffeine comprised more than 85% of the methylated xanthines and methyl uric acids in the urine of infants less than one month of age. These observations indicate a distinct neonatal deficiency in the capacity to metabolise caffeine, and this deficit persists for many weeks since caffeine remained the predominant component in the urine for at least 3 months postnatally. It is intriguing to relate that the adult plasma clearance rate is achieved at 3–4½ months (Table) coincident with the increased capability to produce demethylated metabolites (Aldridge *et al.*, 1979).

The oxidative metabolism of drugs via the cytochrome P-450 mono-oxygenase system is deficient in the human neonate (Aranda *et al.*, 1974; Neims *et al.*, 1976). The relative deficiency with regard to methylxanthine metabolism is greater than seen with other drugs. One subcellular explanation for this difference relates to the existence of multiple forms of cytochrome P-450, each with distinctive substrate specificity and maturational sequence (Thomas *et al.*, 1976; Manchester and Neims, 1977). Caffeine is a good substrate for those form(s) of cytochrome P-450 preferentially induced by polycyclic aromatic hydrocarbons in rats (Welch *et al.*, 1977) and in man. This form of cytochrome P-450 with specific activity for caffeine is probably deficient in the fetus and newborn as suggested by negligible aryl hydrocarbon hydroxylase activity (about 2% of adult value) in the human fetal liver compared with other oxidative enzymes of the mono-oxygenase complex that preferentially metabolise drugs like phenytoin or phenobarbitone (25–50% of adult value) (Pelkonen *et al.*, 1973; Neims *et al.*, 1976).

Phenobarbitone and phenytoin, both known enzyme inducers, were used in one infant (Table) with the highest clearance rate. The possibility that the elimination of caffeine in this infant could have been induced by these drugs exists, but available data suggest that phenobarbitone and phenytoin have little effect on methylxanthine disposition (Greene *et al.*, 1977; Piafsky *et al.*, 1977; Ogilvie, 1978).

The lack of correlation between indices of maturity (gestational age, postnatal age, birthweight) and the kinetic variables (AV_d, $t\frac{1}{2}$, K_{el}, and clearance) during the first 4 weeks of life (Aranda *et al.*, 1979) suggest that elimination does not change during the first few weeks of postnatal life. Shortening of the plasma $t\frac{1}{2}$ starts to occur after the neonatal period and appears to reach adult $t\frac{1}{2}$ by 5–6 months, perhaps to be exceeded thereafter. A much greater clearance rate of drugs in infants after one year of age has been documented with other drugs—such as digoxin (Morselli *et al.*, 1975; Wettrell, 1977; Wettrell and Anderson, 1977) and theophylline (Loughnan *et al.*, 1976; Ogilvie, 1978). Caffeine appears to behave similarly, based on the observations of a 3-fold increase in the mean caffeine clearance rate in the 5- to 6-month-old infant (Table). The fundamental basis for this accelerated clearance rate in older infants compared with adults remains unknown. Similarly, the duration of this accelerated elimination is also not known. The oldest infant studied here was 6 months and ethical consideration has precluded extension of this study to older normal healthy infants.

In summary, our data show that caffeine elimination, unlike that of other drugs, is exceedingly slow in the neonate with tardy maturation to the adult level.

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Effect of puberty on rates of bone growth and mineralisation

With observations in male delayed puberty

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SUMMARY The bone mineral content (BMC) and body height were measured in 301 normal children and adolescents aged 7–20 years, and in 8 boys with constitutional delayed puberty aged 14–17 years. Serum testosterone was measured in the last group as well as in a subpopulation of the normal children and adolescents. The growth spurt, which coincided with a steep increase of serum testosterone in boys, indicated a great change in skeletal growth and mineralisation in both sexes. After the growth spurt, linear growth slowed down considerably while bone mineralisation rose steeply. When low levels of serum testosterone were maintained, as in delayed puberty, these combined changes of skeletal growth and mineralisation did not occur. It is suggested that gonadal hormones are the true initiators of the short-lived growth spurt as well as of prolonged acceleration of bone mineralisation.

Measurement of bone mineral content (BMC) by photon absorptiometry is a precise, reliable, and easy method for assessing skeletal status (Christiansen *et al.*, 1975a). BMC varies with age and sex and the biological variation is greatest during puberty (Christiansen *et al.*, 1975b). In this period of outstanding growth the chronological age may be a poor indicator of physical development, as there is a wide range of growth and sexual maturation in individuals of the same age (Marshall and Tanner, 1970). In boys, serum levels of testosterone correlate well with the pubertal stage (Knorr *et al.*, 1974), and this is a better measure of physical development than chronological age during adolescence. Determinations of serum testosterone and of various indicators of bone status have been used to assess the physical development in the adolescent, but comparisons between BMC and serum testosterone have not been reported.

In order to evaluate skeletal growth and mineralisation in relation to age and development we examined BMC, serum testosterone, and body height in normal boys during childhood and adolescence, and in boys with constitutional delayed puberty.

Patients and methods

Normal children and adolescents. A total of 301 normal children and adolescents aged between 7 and 20 years participated in the study. They were randomly selected from pupils at two schools in a surburban area. Pupils below 18 years obtained written consent from their parents. All were in good health without symptoms of gastrointestinal or renal diseases. None took contraceptive pills or any other type of drug. Data on sex, age, and height are given in Figs 1 and 2.

Boys with delayed puberty. Eight boys, referred to the clinic for delayed growth or delayed pubertal development, or both, were chosen. The diagnosis was constitutional or familial delayed puberty

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(Wilkins, 1965) without signs of other endocrine disease. Based on data on pubertal changes in normal boys (Marshall and Tanner, 1970) the retardation in pubertal development was at least 2 SDs in 6 boys and between 1 and 2 SDs in 2 boys. Testicular size was within the pubertal range in all boys.

Methods

BMC was determined by direct photon absorptiometry (Christiansen *et al.*, 1975a). The forearm was fixed in a plexiglass container filled with distilled water. A source of radiation (25 mCi^{125}I) and a detector were placed on each side of the forearm to be examined. As these moved across the arm the transmission of photons through the bones decreased depending on the bone mineral content. Because the absorption in plexiglass, distilled water, and soft tissue is almost identical, the measurement was independent of the amount of soft tissue. The scanner started distally on the forearm, moving 4 mm proximally between each scan. The first scan was defined as that demonstrating a distance between radius and ulna of at least 2 mm. The bone mineral content was expressed in arbitrary units as a mean of 6 scans on each forearm. The coefficient of variation in normal subjects is about 2%.

From the 156 normal boys, a subgroup of 103 was randomly selected for determination of serum levels of testosterone. Serum testosterone was measured by radioimmunoassay including a modification of thin-layer chromatography (Pirke, 1973).

Results

Normal children and adolescents. Figs 1 and 2 give the heights and BMC values in boys and girls divided into one-year age groups. Before the growth spurt—between ages 11 and 12 years in girls, and 2 years later in boys—the mean height and BMC increments each year were similar in boys and girls. The respective height increments were 4·5 and 4·7 cm per year, while BMC increased very slowly, 0·14 and 0·09 units per year. After the growth spurt linear growth procedeed slowly at average rates of 1·5 and 0·5 cm per year respectively, while there was a large increase in BMC in both sexes. During this phase of development the BMC increments averaged 2·23 units per year in boys and 1·13 units per year in girls (Figs 1 and 2).

Fig. 3 shows the association between serum testosterone and age in the boys. A sharp increase was found at ages 13 and 14 years, simultaneous with the growth spurt (Fig. 1).

Boys with delayed puberty. For their chronological age of 15·9 ± 0·9 years these boys were small, 155·0 ± 4·8 cm, and had very low BMC values averaging 27·2 ± 4·0 units, corresponding to 66%

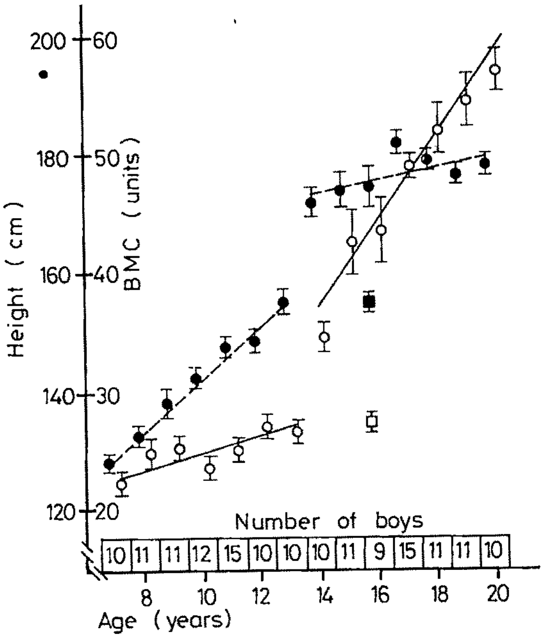

Fig. 1 *Bone mineral content* (o) *and height* (●) *as a function of age in 156 normal boys aged 7–20 years and in 8 boys with delayed puberty* (□ *and* ■). *Values given as mean ± SE of mean.*

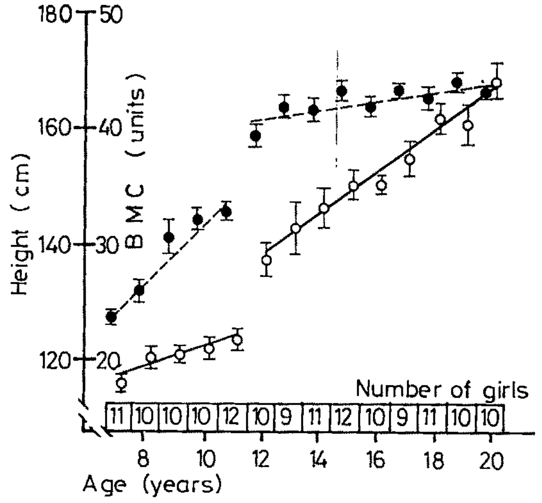

Fig. 2 *Bone mineral content* (o) *and height* (●) *as a function of age in 145 girls aged 7–20 years. Values given as mean ± 1 SE of mean.*

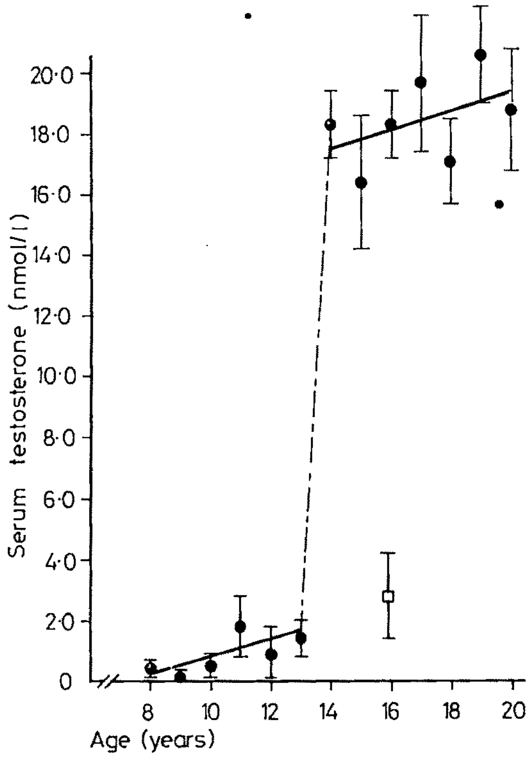

Fig 3. *Serum testosterone levels* (●) *as a function* of *age in 103 normal boys aged 7–20 years and in 8 boys with delayed puberty* (□). *Values given as mean* ± *1 SE of mean.*
Conversion: SI to traditional units—testosterone 1 nmol/l ≈ 0·288 ng/ml.

of age-matched normal boys. Their average level of serum testosterone was also low, 2·8 ± 4·1 nmol/l (0·80 ± 1·18 ng/ml) (Fig. 3). All these values are given as mean ± 1 SD.

Discussion

The onset of the adolescent growth spurt is an important event in skeletal development. In addition to the rather short-lived spurt of growth, it indicates the start of a much more prolonged acceleration of bone mineralisation in both sexes. The timing within the same year of a steep increase of the serum testosterone levels in boys (Fig. 3) with the growth and mineralisation spurt suggests an important role for testosterone in the initiation of both processes and probably in the maintenance over several years of the accelerated bone mineralisation. This view is supported by our observations in boys with delayed puberty: the maintenance of low levels of serum testosterone postpones the onset of the growth and mineralisation spurt. As the peak height increment and the increase in BMC in girls occur at ages 11 to 12 years, when rising levels of plasma oestrone and oestradiol are being observed (Gupta, 1975), it also seems reasonable to assume that rising levels of these hormones serve as the initiator of both spurts in girls. Gonadal hormones may exert their effects on mineralisation through a complex of mechanisms. Firstly, these hormones may have a direct inhibiting effect on bone resorption, although data from tissue culture studies are conflicting (Atkins *et al.*, 1972; Caputo *et al.*, 1976). Secondly, gonadal hormones are potent stimulators of the production of the biologically active vitamin D3 metabolite, 1,25 $(OH)_2$ D_3, in birds (Tanaka *et al.*, 1976), and have also been found to increase plasma calcitonin levels in normal man (Hillyard *et al.*, 1978). Thirdly, androgens may also enhance the skeletal sensitivity to calcitonin, as shown in the rat (Ogata *et al.*, 1970).

The results in the boys with delayed puberty show the importance of using proper reference materials especially in adolescents. If the BMC values are compared with those of age-matched controls, as is done conventionally for the purpose of calcium metabolic investigation, a diagnosis of severe osteopenia would be made. Therefore we suggest that BMC measurements in pubertal boys should be evaluated from testosterone levels or physical development, rather than from chronological age.

Figs 1 and 2 show that the greatest dissociation between skeletal growth and mineralisation takes place during the last years ahead of the growth and mineralisation spurt. This phenomenon may in fact explain the peak incidence of forearm fractures observed in children of 10–14 years of age (Alffram and Bauer, 1962)

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The following articles will appear in future issues of this journal:

Mumps and varicella vaccines. *J. A. Dudgeon.*

Outpatient paediatric cardiological investigation—an alternative approach. *G. J. Williams.*

Effect of nasogastric tubes on nasal resistance during infancy. *J. Stocks.*

Lactobezoar and cows' milk protein intolerance. *J. N. Lemoh and J. Watt.*

Immunological abnormalities in the syndrome of poliomyelitis-like illness associated with acute bronchial asthma (Hopkins's syndrome). *J. I. Manson and Y. H. Thong.*

Poliomyelitis-like illness associated with asthma. *H. K:son Blomquist and B. Björkstén.*

Archives of Disease in Childhood, 1979, **54**, 954–957

Lymphocyte changes in β-thalassaemia major

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SUMMARY Lymphocyte subpopulations were studied in 20 hypertransfused patients with β-thalassaemia major, some of whom had been splenectomised. B-lymphocytes were normal but T-lymphocytes were decreased in all patients. The T-cell count was lower in the splenectomised patients than in the nonsplenectomised ones. In the former, the active rosette-forming lymphocytes were also diminished, but the difference was not significant. In all patients the percentage of null cells was greater and the activity of K-cells increased compared with controls.

Many patients with β-thalassaemia develop chronic liver disease (Ellis *et al.*, 1954; Panizon and Vullo, 1957; Beltrami and Nenci, 1969; Masera and Jean, 1973). This complication has been attributed to hepatitis virus infection in a liver already stressed by the iron overload (Masera and Jean, 1973; Masera *et al.*, 1976). As chronic hepatitis may be related to an immunological dysfunction, we studied the lymphocyte subpopulation in a group of patients with thalassaemia major. A decreased proportion of T-cells associated with greater K-cell activity is reported.

Methods

20 patients, aged between 3 and 22 years, with thalassaemia major were studied. Eight had undergone splenectomy. Each was regularly transfused with packed red cells every 20–30 days in order to maintain Hb>9 g/dl. 12 normal subjects, aged between 3 and 12 years, served as controls. Serum transaminases were determined; Hb_sAg and Hb_sAb by the solid radioimmunoassay method (AUSRIA II and AUSAB); immunologlobulin levels and C3 and C4 components of serum complement by single radial immunodiffusion, using specific antisera (Kallestad). Purified lymphocytes were obtained by fractionation of heparinised blood on a Ficoll-Hypaque density gradient (MSL Eurobio). In some experiments residual phagocytic cells were eliminated by incubating the cells with iron powder and removing the phagocytic ones with a magnet. T-lymphocytes were identified by sheep red cell rosetting (SRCR) technique (Jondal *et al.*, 1972) and active rosette-forming lymphocytes were identified by the method of Wybran *et al.* (1972), modified by Horowitz *et al.* (1975). B-lymphocytes were identified by the presence of fluorescence on their surfaces when treated with antiwhole immunoglobulin conjugate (Kappel Laboratories), using the technique of Permis *et al.*, 1970. K-cell activity was measured by ^{51}Cr-labelled chicken red blood cell (CRBC) technique. Antibodies against chicken red cells were obtained in rabbits by injecting them with 1 ml 10% CRBC suspension twice weekly for 3 weeks. For the assay, CRBC (0·2 ml) were labelled with 100 μCi of ^{51}Cr sodium chromate for 30 min at 37°C. After incubation, the red cells were washed 3 times with RPMI 1640 and diluted to a concentration of $2{\cdot}5 \times 10^6$/ml. Then 0·1 ml of the lymphocytes at a concentration of $5{\cdot}0 \times 10^6$/ml was placed in a plastic tube containing 0·5 ml inactivated antibody at a dilution of 1:1000, 0·2 ml ^{51}Cr-labelled red cells, and 1·7 ml tissue culture medium. All the dilutions were made in RPMI 1640, supplemented with 10% fetal calf serum previously absorbed with CRBC. Control incubations were carried out in the absence of antibodies or lymphocytes, and a second control tube containing labelled red cells and distilled water was included in the experiment. After incubation overnight at 37°C, the tubes were gently centrifuged, the supernatant collected, and radioactivity of the supernatant measured.

Cytotoxicity was evaluated according to the formula:

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$$\frac{(^{51}\text{Cr sample tube})-(^{51}\text{Cr control tube})}{(^{51}\text{Cr distilled water})-(^{51}\text{Cr control tube})}\times 100$$

The spontaneous release of ^{51}Cr was always <10% in the control tube.

Results

The serological data for 20 hypertransfused patients are listed in Table 1. An increase in serum transaminases was observed in both groups, particularly in the splenectomised patients. IgA and IgG immunoglobulins were also increased in the thalassaemic patients, again particularly in the splenectomised ones. C3 and C4 in thalassaemic patients were normal, but C3 was slightly low in splenectomised patients. The Hb_sAg and Hb_sAb tests gave one Hb_sAg positive and 11 Hb_sAb positive, the remaining 8 patients had negative results. Eight patients developed a typical icteric hepatitis B. B- and T-lymphocyte assay and K-cell activity in the thalassaemic patients and controls are shown in Table 2 and the Figure. Regularly transfused patients had normal B-lymphocytes but fewer T-lymphocytes than controls. The T-cell count was lower in the splenectomised than the nonsplenectomised patients (P<0·005). The active rosette-forming lymphocytes were also diminished, but this difference was not significant.

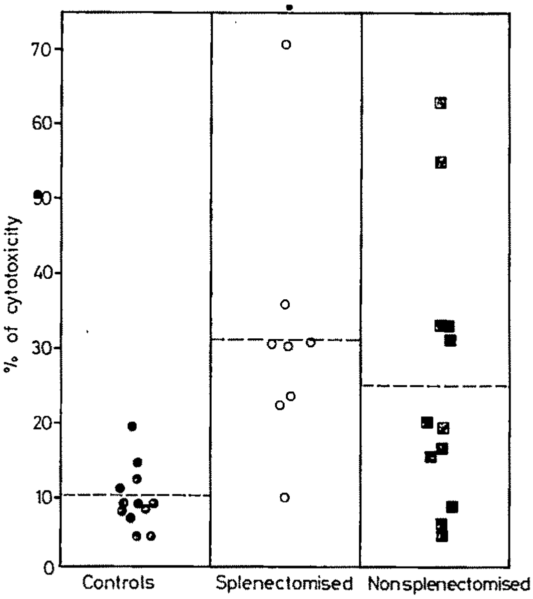

Figure *Antibody-mediated cytotoxicity to CRBC of lymphocytes from 12 normal controls and 20 patients with β-thalassaemia major. Normal controls 10·35 ± 4·34; splenectomised patients 32·88 ± 17·95; nonsplenectomised patients 25·89 ± 18·81.*

Table 1 *Serological data (means ± SD) for 20 patients with β-thalassaemia major*

	Sex				*Transaminases*		*Immunoglobulins*			*Complement*	
	Male	*Female*	*Age (years)*	*Hb (g/dl)*	*AST (mU)*	*ALT (mU)*	*IgA (IU/ml)*	*IgM (IU/ml)*	*IgG (IU/ml)*	*C3 (g/l)*	*C4 (g/l)*
Normal values				13·84 ±1·05	0–12	0–12	83·30 ±42·84	116·15 ±48·30	11·46 ±3·75	1·13 ±0·32	0·27 ±0·07
β-Thalassaemia, splenectomised (n = 8)	4	4	13·75 ±6·31	9·81 ±1·16	64·75 ±27·42	41·25 ±19·91	219·15 ±114·18	198·51 ±123·42	21·33 ±6·73	1·01 ±0·14	0·18 ±0·07
β-Thalassaemia, nonsplenectomised (n=12)	4	8	5·50 ±1·93	9·00 ±1·88	32·00 ±12·68	24·16 ±20·60	76·30 ±40·74	178·88 ±128·05	14·94 ±5·69	0·94 ±0·18	0·22 ±0·05
Total β-thalassaemia (n = 20)	8	12	8·80 ±5·84	9·33 ±1·65	45·10 ±25·32	31·00 ±21·60	133·44 ±104·50	206·65 ±124·43	17·49 ±6·77	0·97 ±0·17	0·20 ±0·06
P (Student's *t* test)	1 ——→ 2		<0·0025	<0·15	<0·0025	<0·05	<0·0005	<0·40	<0·025	<0·20	<0·15

Table 2 *Lymphocytes (means ± SD) in 12 normal controls and in 20 patients with β-thalassaemia major*

	Lymphocytes (%)				*Lymphocytes (10^9/l)*			
	B-	*T-*	*Null*	*Active RF**	*B-*	*T-*	*Null*	*Active RF**
Controls (n = 12)	18·66 ±5·06	60·41 ±4·36	20·00 ±6·86	46·88 ±10·68	764·75 ±400·02	2447·16 ±962·45	896·00 ±482·01	1833·72 ±762·87
β-Thalassaemia, splenectomised (n = 8)	19·75 ±9·28	39·00 ±9·35	41·25 ±13·04	38·00 ±9·84	577·37 ±383·63	1106·37 ±407·69	1197·37 ±552·91	1012·37 ±298·91
β-Thalassaemia, nonsplenectomised (n = 12)	19·83 ±9·24	47·66 ±9·63	33·83 ±14·70	39·25 ±6·15	787·58 ±634·50	1948·25 ±750·91	1462·16 ±1022·90	1622·91 ±715·88
Total β-thalassaemia (n = 20)	20·00 ±9·16	44·20 ±10·24	36·80 ±14·20	38·25 ±8·49	703·50 ±377·23	1611·50 ±752·82	1356·25 ±857·97	1378·70 ±650·99
P (Student's *t* test)	1→4 2→3				<0·35 <0·15	<0·01 <0·005	<0·05 <0·30	<0·05 <0·025

*RF = Rosette-forming.

The percentage of null cells was significantly higher in the thalassaemic patients compared with controls, but the splenectomised did not differ from nonsplenectomised patients in this respect.

The activity of K-cells in the 20 hypertransfused patients was increased ($P<0\cdot0025$) compared with controls, but there was no difference between splenectomised and nonsplenectomised patients ($P<0\cdot25$). This increased K-cell activity was unaffected when phagocytes were removed with a magnet so that the greater activity did not appear to be caused by contamination with monocytes and polymorphs.

Discussion

Our study shows that a decrease of T-lymphocytes takes place in patients with β-thalassaemia major. This decrease is also reflected in the number of active rosette-forming lymphocytes. Wyler (1976) observed lower T-cell counts in children with splenomegaly due to malaria; he suggested that the T-cell lymphopenia was due to selective sequestration of T-lymphocytes in the spleen. However, our splenectomised patients had a lower mean T-cell count than nonsplenectomised ones. These results seem to exclude the spleen from a role in the depletion of T-lymphocytes. As our results give no evidence that the presence of a serum factor interferes with rosette formation, the mechanism of T-lymphocyte depletion in β-thalassaemia remains unknown.

The selective depletion of T-lymphocytes in β-thalassaemia seems to be unassociated with impairment of cell-mediated immunity (Kanakoudi-Tsakalidis *et al.*, 1977). It could be due to a depletion of particular T-cells, perhaps suppressor T-cells. Such a depletion of suppressor T-cells may contribute to the increased production of immunoglobulin observed in hypertransfused patients (a normal percentage of B-circulating lymphocytes was noted).

Casali *et al.* (1978) observed an increase in circulating soluble immunocomplexes in thalassaemics treated with multiple transfusions, related to the age of the patient; complement levels were also decreased. This increase of immunocomplexes seems to be a consequence of the development of chronic hepatitis due to HB virus or to iron overload, or both (Masera and Jean, 1973; Masera *et al.*, 1976). The immunocomplexes in β-thalassaemia could also occur through the isoantigen antibodies complexes due to blood transfusion (Pearson and O'Brien, 1975). Such immunocomplexes may stimulate K-cell activity, the greater number of null cells being then due to the increased number of K-cells.

It is not known whether the increased activity of K-cells is due to an increase in cytotoxic activity of individual cells or to an increase in cell number. Increased K-cell activity has been observed only in hypertransfused patients and is directly related to the age of the patient. Whether or not the patients had been splenectomised seemed to be immaterial, despite the fact that the splenectomised patients were significantly older than the nonsplenectomised ones. Increase of K-antibody-dependent cells was observed in chronic active hepatitis by Cochrane *et al.* (1976) and also in many acute and chronic liver diseases of infancy (Smith *et al.*, 1977). The presence of increased K-cell activity in β-thalassaemia suggests that these cells may play a key role in the cirrhosis affecting thalassaemic children.

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Change of reference style

From January 1980, the *Archives* will change its style for citing references and will follow the number system. We are making this change in order to conform with the 'Vancouver style' of uniform requirements for manuscripts submitted to biomedical journals.

Previously the *Archives* has used the Harvard reference system. Its advantages and disadvantages compared with those of the number system have seemed evenly balanced, but the editors have been aware of the burden imposed on authors and their secretaries by the different styles which different journals require. Therefore, with the unanimous agreement of the editorial committee, we have decided to support a move whereby a large—and increasing—number of major medical journals will accept manuscripts presented in one agreed style.

The system numbers references consecutively in the order in which they are first mentioned in the text. References are identified in the text by arabic numerals. For further details see instructions to authors inside the front cover, and the references cited.[1,2]

From now onwards all manuscripts submitted should accord with the new style.

[1] International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979; **1**: 533–535.

[2] Lancet. The Vancouver style. Uniform requirements for manuscripts submitted to biomedical journals. *Lancet* 1979; **1**: 429–430.

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Concentration of zinc in the hair of schoolchildren

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SUMMARY The concentration of zinc in the hair of 219 schoolchildren aged between 10 and 11 years was measured and related to height, weight, estimates of consumption of zinc-rich foods, number of children living at home, and rank in family. None of the correlation coefficients between hair zinc and the other variables was significant. Mean concentration of zinc was higher ($P<0\cdot001$) in the girls (146 µg/g; 2·23 µmol/g) than in the boys (118 µg/g; 1·81 µmol/g). Eight children (3·7% of the total) had <75 µg/g (<1·15 µmol/g) zinc in their hair but only one of them was below the 10th centile for height or weight—a girl with coeliac disease.

A condition of zinc deficiency associated with dwarfism and hypogonadism was first observed in young adult men in Iran (Prasad *et al.*, 1961), and Egypt (Prasad *et al.*, 1963), and it was later reported in 2 young Iranian women (Ronaghy and Halsted, 1975). Zinc deficiency has also been identified in adolescent boys in the Middle East (Ronaghy *et al.*, 1974), and in boys and girls in the USA (Hambidge *et al.*, 1972), but no reports have been published of zinc deficiency in any normal British population.

Zinc deficiency in children before the age of puberty is characterised by retarded growth, poor appetite, and loss of taste acuity (hypogeusia). Hambidge *et al.* (1972) considered that a hair zinc concentration of <70 µg/g (<1·07 µmol/g) represented marginal zinc deficiency, and in a group of 132 children aged between 4 and 16 years in Denver, Colorado, 10 had hair zinc concentrations lower than this. Eight of these children had heights at or below the 10th centile on the Iowa growth charts and 5 responded to treatment with zinc.

Methods

Since the concentration of zinc in hair is often used as an index of zinc-status, we undertook a survey of the zinc content of the hair of 10- to 11-year-old children to see whether or not a deficiency of zinc could be detected. The children came from four different schools in the Southampton area. All the children (403) in this age group were invited to participate in the survey, and 219 agreed. With the exception of 2 Negro children and one Indian child, all were white, The heights and weights of the 219 children were measured, and 157 of them returned the diet sheet and simple questionnaire which they had been asked to complete. The questionnaire contained questions about the date of birth of the child, heights and occupation of the parents, the rank of the child in the family, and whether or not he or she had school meals or was on a special diet (for example, for reasons of health or religion).

Rough estimates of zinc intake were made by classifying foods into 5 categories according to zinc content, class 1 foods (for example fruit, leafy vegetables, butter) containing the smallest amounts of zinc and class 5 (for example, lamb, beef) containing the greatest, and calculating the weight for each category of food eaten.

Samples of hair (10–20 mm in length and weighing about 500 mg) were taken close to the skin from the same region of the nape of the neck for each child; these were then cut into lengths of 1–2 mm with scissors. After exhaustive washing with acetone, detergent solution (sodium lauryl sulphate, 100 g/l), and distilled water in sequence, followed by a final rinse in acetone, the hair samples were air dried between filter paper. Duplicate samples of approximately 100 mg were digested in 2 ml concentrated nitric acid of a special grade, low in trace elements at 85°C for 2 hours in a stoppered tube. After cooling, the digests were made up to 25 ml with glass-distilled water and analysed for zinc by atomic absorption spectrophotometry. Analysis of 13 replicate samples from the hair of one individual gave values with a coefficient of variation of 6%.

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Results

Correlation coefficients were calculated for each sex between individual hair zinc values and height, weight, number of children living at home, rank in family, and consumption of the different categories of zinc-containing food, and none of these coefficients was statistically significant. The correlation coefficients between number of children living at home and height (−0·37) and weight (−0·41) were, however, significant ($P<0{\cdot}01$) as were the correlations between rank in family and height (−0·21), and maternal and child's height (+0·23).

The mean hair zinc concentration was higher in girls than boys ($P<0{\cdot}001$) (Table 1). This large sex difference has not been reported previously in children, probably because no other studies have been carried out with such large numbers of children over such a narrow age range. The distribution of hair zinc values was normal (Table 2). The mean values are similar to those reported by Klevay (1970) for this age group in Panama, but are somewhat lower than the values observed by Hambidge *et al.* (1972) for American children. Eight children, 6 boys and 2 girls, had <75 µg/g zinc in their hair but only one of these children was below the 10th centile for height or weight—a girl with coeliac disease.

14 children were found with heights at or below the 10th centile and 19 had weights below this centile but, apart from the girl with coeliac disease, none had hair zinc <90 µg/g (<1·38 µmol/g). There was thus no evidence that short stature and low weight were associated with zinc deficiency, or indeed that the deficiency of zinc suggested by low hair zinc was sufficiently serious to depress growth. All the diet sheets available for the normal children in these subsamples suggested that their diets were adequate in both quality and quantity, but the records were not sufficiently detailed to permit any accurate calculations of actual zinc intakes to be made.

Table 1 *Concentration of zinc in the hair of 10- to 11-year-old schoolchildren*

		Concentration (µg/g)		
		Mean	*Range*	*SEM*
Boys	(n = 92)	118	30–189	3·1
Girls	(n = 127)	146*	70–235	2·8

Conversion: traditional units to SI—1 µg/g ≈ 0·0153 µmol/g
*Significantly greater than the mean for the boys ($P<0{\cdot}001$, Student's *t* test).

No assessment was made of the stage of sexual development of the children but it was clear from their heights and weights that whereas most of the girls had entered the adolescent growth spurt, only a few of the boys had done so. Only 6 of the 127 girls had reached the critical weight of 48 kg which Frisch and Revelle (1971) have related to the menarche. The range of hair zinc of these 6 girls was 90–200 µg/g (1·38–3·06 µmol/g), a mean of 139 ± 15·5 µg/g (SEM) (2·13 ± 0·24 µmol/g), indicating that this subgroup did not differ significantly from the whole population.

Discussion

There was no evidence of a serious deficiency of zinc in these 219 normal children, despite the fact that 3·7% of them had concentrations of zinc in their hair within the range commonly accepted as indicative of a marginal deficiency.

Requirements for zinc increase at puberty, particularly in boys, presumably associated with the high concentration of zinc present in the testes and accessory male sex glands (Mawson and Fisher, 1953), and a deficiency of this element appears to be more common in males than in females. In this context it is interesting to note that the mean hair zinc concentration was lower in the boys than the girls in this series, suggesting that boys may have smaller body reserves of zinc than girls to support the increased demands of puberty.

A similar sex difference in hair zinc concentration has recently been reported among New Zealand students aged between 18 and 27: in that study the mean hair zinc in the male subjects was 180 ± 3·9 (SEM) µg/g (2·75 ± 0·06 µmol/g) and in the females 195 ± 3·1 µg/g (2·83 ± 0·05 µmol/g) ($P<0{\cdot}01$) (McKenzie, 1979).

A major problem in using hair as a biopsy material for the assessment of trace element status is the danger of contamination by extraneous matter, particularly by cosmetics; whereas superficial 'dirt' is readily removed by efficient washing, lacquers and dyes may be impossible to remove completely by

Table 2 *Distribution of zinc concentrations in the hair of 10- to 11-year-old schoolchildren*

	Zinc concentration (µg/g)								
	25–49	*50–74*	*75–99*	*100–124*	*125–149*	*150–174*	*175–199*	*200–224*	*225–250*
Boys	2	4	16	28	31	9	2	0	0
Girls	0	2	9	15	45	35	16	3	2

See Table 1 for conversion to SI units.

normal washing. We were certainly aware of these problems and renewed each portion of wash liquid until it remained absolutely clear and colourless, but no comparisons were made between the zinc content of unwashed samples and samples at different stages of the washing process. Although the possibility that the sex difference observed in hair zinc concentrations was due to the greater use of zinc-containing cosmetic preparations by the girls cannot be ruled out entirely, this explanation seems rather unlikely in view of the age of the children, particularly as our mean values were somewhat lower than those reported for American children. Furthermore, McKenzie (1978) showed that treatments such as dyeing, bleaching, and cold waving decrease the zinc concentration of hair. Nevertheless, in retrospect, we wish we had included a question on the use of hair preparations in our questionnaire.

Further studies should be carried out on the zinc status of older children and adolescents. In the Middle East, zinc deficiency is thought to be conditioned by the high phytate content of the staple food of the population, unleavened whole-wheat bread, and the zinc nutrition of the children of Asian immigrants in Britain, many of whom are vegetarians and whose diet includes chappatis made from flour rich in phytate, merits particular study.

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Short reports

Cerebrospinal fluid immunoglobulins in children

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SUMMARY Cerebrospinal fluid (CSF) immunoglobulins were measured in 62 normal children, in 9 children with purulent meningitis, and in 10 children with presumptive viral meningitis. The mean values in normal children were IgA 0, IgM 0, and IgG 0·84 ± 1·4 mg/100 ml (± SD). The mean levels of all CSF immunoglobulins were raised in acute bacterial meningitis and were significantly greater than the levels found in viral meningitis. CSF IgM was 0·16 ± 0·5 mg/100 ml in viral meningitis compared with 2·64 ± 2·06 mg/100 ml in bacterial meningitis ($P<0·01$). However, these values overlapped to a considerable extent and, generally, measurement of CSF immunoglobulins did not enhance diagnostic accuracy in this group of children.

Smith *et al.* (1973) presented data on CSF immunoglobulins in meningitis in adults, and suggested that the levels of IgM might help to distinguish viral from bacterial meningitis.

Methods and material

CSF immunoglobulins were measured in 81 children aged between 0·1 and 10½ years. The indications for spinal tap were meningitis, suspected meningitis, convulsions, or (for therapeutic purposes) leukaemia. The 62 children designated as normal had WBC <10 × 10^6/l (<5 × 10^6/l in all except 4), and normal CSF protein and glucose relative to age. Most of the children were being evaluated for suspected meningitis or because they had had febrile convulsions. Nine children were considered to have bacterial meningitis, of which 3 proved to be due to *Haemophilus influenzae*, 3 to *Neisseria meningitidis*, 1 to *Staphylococcus albus*, and 2 showed no growth on culture. In 10 children meningitis was presumed to be viral in origin on the basis of leucocyte response, CSF protein and glucose levels, and clinical course. Specific viral cultures were not performed.

Lumbar puncture was performed as indicated on admission and the CSF analysed routinely in the laboratory. An unspun aliquot of the CSF was stored at 4°C before the immunoglobulins were estimated. CSF immunoglobulins were measured without knowledge of the child's clinical or routine CSF findings. Cerebrospinal fluid samples which were grossly blood-stained or which contained RBC >100 × 10^6/l were discarded.

CSF immunoglobulins concentrations were measured by the radial immunodiffusion method (Mancini *et al.*, 1965), using commercial L.C. Partigen plates and pooled human serum (Behring) as standard. 5 μl centrifuged, undiluted CSF was placed in the application wells and incubated for 72 hours at room temperature. Appropriate dilutions of standard in normal saline were also prepared. To intensify the precipitin ring the IgM and IgA plates were rinsed in phosphate-buffered saline for 24 hours, then covered with a 4% aqueous solution of tannin for 30 minutes and washed with distilled water. Standard curves were prepared from the square of the precipitin rings.

Results

Table 1 shows that IgA and IgM were not detected in

Table 1 *Clinical and CSF findings in 81 children (mean ± SD)*

	Normal CSF (n = 62)	*Viral meningitis (n = 10)*	*Bacterial meningitis (n = 9)*
Mean age (years)	2·4	5·1	1·5
(Range)	(0·1–10·0)	(0·7–10·5)	(0·3–4·5)
WBC (× 10^6/l)	1·95 ± 2·0	148·1 ± 91·5	2352·1 ± 2756·0
Polymorphs (%)	—	43·4 ± 29·3	70·6 ± 29·9
Lymphocytes (%)	—	56·6 ± 216	29·4 ±32·4
Protein (mg/100ml)	12·9 ± 9·6	31·0 ± 28·5	163± 120·3
Glucose (mg/100 ml)	59·7 ± 16·7	63·8 ± 15·4	15·1 ± 16·3
IgA mg/100 ml	0·0	0·0	1·89 ± 2·2
IgM mg/100 ml	0·0	0·16 ± 0·5	2·64 ± 2·06
IgG mg/100 ml	0·84 ± 1·4	4·19 ± 9·1	17·88 ± 6·21

Conversion: traditional units to SI—CSF proteins: 1 mg/100 ml ≈ 0·01 g/l, glucose: 1 mg/100 ml ≈ 0·0555 mmol/l.

the CSF of normal children, 69% of whom were aged under 3 years; IgG ranged from 0·1 to 3·6 mg/100 ml with a mean IgG level of 0·84 mg/100 ml. In the 10 children with viral meningitis, IgM was undetectable in 9 children and present in a concentration of 1·6 mg/100 ml in one child; IgM was undetectable in 2 children with bacterial meningitis, and in the remainder it ranged from 0·75 to 5·1 mg/100 ml (mean 2·64). IgG levels were raised in excess of 5 mg/100 ml in 7 of 9 children with bacterial meningitis. The mean levels of all CSF immunoglobulins, particularly IgG, were significantly higher in bacterial than in viral meningitis (Table 2).

Discussion

It is known that serum immunoglobulins are lower in children than in adults. At age 1–2 years serum IgG, IgM, and IgA are 66, 59, and 25% of respective adult values (Stiehm and Fudenberg, 1966). It is believed that CSF immunoglobulins are derived by diffusion from serum, although the lymphoid tissue may produce IgG (Lord *et al.*, 1973).

Table 2 *Significance in the differences (mean ± SD) in distribution of CSF substances in three groups of children using the Mann-Whitney U test*

CSF	*Normal v. viral*	*Normal v. bacterial*	*Viral v. bacterial*
Protein	$P<0·01$	$P<0·01$	$P<0·01$
Glucose	NS	$P<0·01$	$P<0·01$
IgA	NS	$P<0·01$	$P<0·05$
IgM	NS	$P<0·01$	$P<0·01$
IgG	$P<0·05$	$P<0·01$	$P<0·05$

In the present study a statistically significant difference in CSF IgG levels was shown between normal children and those with viral or bacterial meningitis, although the levels overlapped. High levels of CSF IgG (>5 mg/100 ml) were found in 7 children, and high levels of IgM (>3 mg/100 ml) in 5 of 9 children with bacterial meningitis.

Retrospectively, CSF immunoglobulins did not enhance the diagnostic accuracy of acute childhood meningitis as similar information could be gained from study of the total differential white cell count in combination with protein and glucose analyses (Table 1).

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Treatment of a neonate with propionic acidaemia and severe hyperammonaemia by peritoneal dialysis

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SUMMARY A moribund newborn infant with propionic acidaemia and severe hyperammonaemia was successfully treated by peritoneal dialysis. The removal of ammonia and possibly additional toxic metabolites by peritoneal dialysis may be life-saving in newborn infants with propionic acidaemia or other hyperammonaemic syndromes.

Propionic acidaemia is a rare inborn error of metabolism which can be present in the neonatal period with persistent ketoacidosis and altered neurological status (Rosenberg, 1978). Survival of an infant thus affected depends on rapid diagnosis and immediate institution of measures to alleviate the chemical imbalances accompanying the disease. The usual treatment is to restrict the proteins while maintaining adequate calories and fluids to prevent the accumulation of harmful metabolites, but occasionally deterioration of the condition of the patient necessitates more drastic removal of these metabolites. We report a case of a neonate with propionic acidaemia who had extremely high blood ammonia concentrations with coma, but who survived after the rapid removal of ammonia by peritoneal dialysis.

Case report

A 3-kg baby girl, born at term after an uncomplicated pregnancy to a 27-year-old mother, was the only child of nonconsanguineous parents. She did well initially and was breast fed for the first days of life. Tachypnoea (>80/min) was noted on the second day of life (Figure) and hepatomegaly on the third, when the baby was transferred to Boston Children's Hospital Medical Center.

On admission (day 3), arterial blood–gases showed a metabolic acidosis with a compensatory respiratory alkalosis—pH 7·30, Po_2 110 mmHg (14·6 kPa), Pco_2 12 mmHg (1·6 kPa), total CO_2 6 mmol/l. White blood cell and platelet counts were normal. Chest *x*-ray was normal. Serum electrolytes were Na 144, K 4, and Cl 103 mmol/l, resulting in an anion gap of 39 mmol/l, indicating severe metabolic acidosis. The baby had protracted hypoglycaemia which required dextrose infusion, initially at 6 mg/kg per min, to maintain a blood glucose concentration of 100–200 mg/100 ml (5·5–11 mmol/l). When the dextrose infusion was stopped there was a fall in blood glucose within 30 minutes to 27–36 mg/100 ml (1·5–2·0 mmol/l), a level which persisted for more than 2 hours. Thereafter, dextrose infusion at 8 mg/kg per min was required to maintain normoglycaemia. Additional studies included a urine dinitrophenylhydrazine test which was positive for α-keto acids and urine, and plasma amino-acid profiles which were within normal limits. Plasma glycine was 432 mmol/l (normal, 120–560 mmol/l).

On day 4, the baby was flaccid and had sustained ankle clonus. There was no evidence of infection. Because of this change in her previously normal neurological status and the evidence of a metabolic disorder, blood ammonia was determined and was noted to be high at 150 µg/100 ml; 83 µmol/l (normal, less than 50 µg/100 ml; 28 µmol/l). On day 5, her blood ammonia level rose to 350 µg/100 ml (194 µmol/l). She became stuporous in spite of vigorous hydration and adequate caloric administration with dextrose. Attempts to perform an exchange transfusion were unsuccessful.

Therefore, peritoneal dialysis was started, cycling 150 ml each hour with an intra-abdominal dwell time of 30 minutes (dialysis solution per litre: Na 132, Cl 102, K 3·5, Ca 10, Mg 1·5, HCO_3 25 mmol/l, dextrose 15 g, pH 6·8). During the 8th cycle, the respiration arrested and was subsequently maintained by assisted ventilation for approximately 27 hours. At the time of her respiratory arrest, the baby was in coma, with fixed dilated pupils, no spontaneous respirations, and absent reflexes. Blood ammonia shortly after the arrest was 1350 µg/100 ml (748 µmol/l). EEG was consistent with severe toxic encephalopathy.

Despite the baby's condition, dialysis was continued. Subsequent measurements of blood ammonia before and after a dialysis cycle showed a decrease of approximately 100 µg/100 ml (55 µmol/l) during the cycle. At 15 hours, she was no longer acidotic. She then began to move spontaneously, and there was gradual neurological improvement. After 30 dialysis cycles (late on day 6), ammonia level was 150 µg/100 ml (83 µmol/l) and dialysis was stopped. She breathed spontaneously and had reactive pupils. She was extubated on the morning of day 7.

On the 8th day, she was started on a low protein diet, 100 kcal/kg (0·5 g/kg per day) with 50% of her calories as even short-chain triglycerides. Results of gas–liquid chromatography and mass spectrometry* of the urine showed the presence of 3-hydroxypropionic acid, methylcitrate, tiglylglycine, and

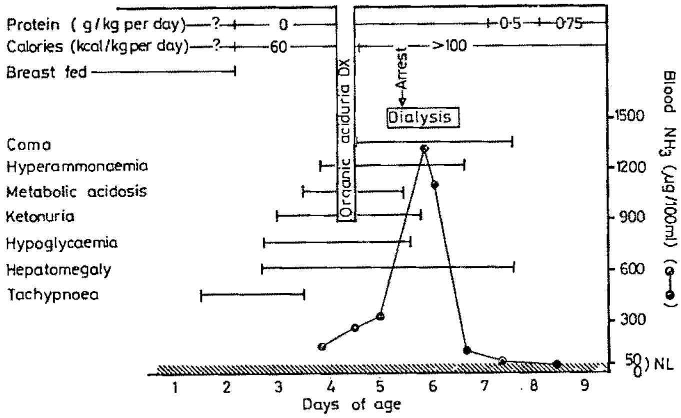

Figure *Course of patient with propionic acidaemia. Clinical events are noted on the right side and nutritional ones across the top. Blood ammonia concentrations are shown on the left ordinate with the normal range shaded. Age of the patient in days is given along the abscissa.*
Conversion: traditional units to SI—
ammonia: 1 µg/100 ml ≈ 0·554 µmol/l.

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*Performed by Dr C. Costello, Massachusetts Institute of Technology, and Dr K. Tanaka, Yale University.

propionylglycine, findings appropriate to the diagnosis of propionic acidaemia. She was therefore empirically started on 5 mg per day biotin orally, which was stopped when her defect was clearly defined by enzyme studies to be nonresponsive to biotin. She became increasingly alert, and was discharged from the hospital on day 12. Her daily diet consisted of 0·95—1·0 g protein/kg and 120 kcal/kg.

Since discharge, she has had several viral illnesses with associated metabolic acidosis, ketonuria, and a peak blood ammonia of 170 μg/100 ml (94 μmol/l); these have required parenteral treatment with fluids and a short time in hospital. Otherwise, she has remained in good metabolic control and has gained weight, being 6·6 kg at 15 months. Unfortunately, she developed an athetoid disorder during her second viral illness and her developmental milestones are delayed.

Fibroblast and leucocyte enzyme analysis

Propionyl CoA carboxylase (PCC) and β-methylcrotonyl CoA carboxylase (β-MCC) activities were measured in isolated peripheral leucocyte extracts and in skin fibroblast cultures established from the patient and her parents as previously described (Wolf and Rosenberg, 1978). As shown in the Table, the patient has deficient propionyl CoA carboxylase activity both in her fibroblast and leucocyte extracts. PCC activities in fibroblast and leucocyte extracts from both parents were intermediate between deficient and control values, whereas β-MCC activities in fibroblast extracts from the patient and her parents were normal. The patient's PCC was not stimulated by incubating her fibroblast cultures in medium containing 10 mg/ml biotin for 4 days. Fibroblasts from the patient were assigned to the A complementation group (Gravel *et al.*, 1977).

Table *Propionyl CoA carboxylase and β-methylcrotonyl CoA carboxylase activities (pmol/min per mg protein) in leucocyte and fibroblast extracts of patient and parents*

	Leucocyte	*Fibroblast*	
	*PCC activity**	*PCC activity*	*β-MCC activity*
Patient	4	17	297
Mother	178	399	295
Father	210	559	340
Controls (n = 8)	349 ± 51*	863 ± 102*	283 ± 32*

*1 SD.

Discussion

The importance of rapid diagnosis of inborn errors of metabolism cannot be overemphasised. Our patient was 4 days old and semicomatose when hyperammonaemia was first noted. Persistent metabolic acidosis, ketonuria, and progressive deterioration in neurological status were all clues that the patient had a metabolic disorder. Tachypnoea, which developed during the period of breast-milk feeding, and hyperammonaemia pointed towards protein intolerance.

The presence of propionate metabolites in the urine suggested propionic acidaemia, the result of deficient activity of the enzyme propionyl CoA carboxylase that normally catabolises propionate to methylmalonate. The absence of raised propionate itself in the urine is probably due to its being metabolised via minor pathways and its conjugation with glycine, which is usually raised in the plasma and urine of patients with propionic acidaemia. The normal value of glycine in our patient was unusual and misleading. However, previous cases of propionic acidaemia with intermittently normal concentrations of glycine have been reported (Wadlington *et al.*, 1975). Furthermore, although most patients with propionic acidaemia have normoglycaemia, occasionally a case may demonstrate slight hypoglycaemia (Rosenberg, 1978); our patient, however, exhibited severe hypoglycaemia. The mechanism causing decreased blood glucose is not known but may involve the inhibition of gluconeogenesis.

In addition to propionic acid and glycine, ammonia concentrations may be raised in the blood of patients with propionic acidaemia. Hyperammonaemia, as seen in urea cycle disorders, Reye's syndrome, or hepatic failure, and ketoacidosis, as seen in diabetes, most certainly contributed to our patient's comatose state. Propionate, which unfortunately was not measured in our patient, or its metabolites, may also have primary or secondary toxicity.

Instituting a low-protein diet, sufficient carbohydrates, and even-chain triglycerides is essential, and is usually sufficient to achieve a homeostatic metabolism in patients with propionic acidaemia (Brandt *et al.* 1974). Our patient's rapid and severe neurological deterioration required more drastic therapy, peritoneal dialysis, to remove the toxic agents, but the fact that dialysis for 30 hours was required to return the ammonia level to normal suggests that our patient continued to produce ammonia probably by catabolism of her own protein. We cannot, however, exclude the harmful effect of a respiratory arrest in increasing the blood ammonia concentration or the beneficial effect of assisted ventilation in reducing the blood ammonia concentration. Peritoneal dialysis was previously used by Russell *et al.* (1974) to remove propionate from a severely ill infant with propionic acidaemia, but the ammonia levels were not measured. Peritoneal diaylsis has been used unsuccessfully to treat the severe hyperammonaemia associated with a patient with ornithine transcarbamylase deficiency (Siegel and Brown, 1973). The peak level of ammonia recorded for our patient is the highest yet reported in a patient with propionic acidaemia. This case is presented as the first successful demonstration that peritoneal dialysis together with protein restriction, adequate hydration, and sufficient caloric intake can be life-saving in propionic acidaemia even after the affected newborn has become moribund.

Note added in proof. At age 20 months, the patient developed a viral gastroenteritis, severe metabolic acidosis, and died.

We thank Dr L. E. Rosenberg for help with this patient.

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Transient infantile hyperthyrotropinaemia

Report of a case

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SUMMARY A case of transient hyperthyrotropinaemia was found by mass screening for neonatal hypothyroidism using the paired TSH assay method. The patient was a baby boy born at term after a normal pregnancy who grew without any abnormal signs or symptoms. For the first 7 months after birth, his serum TSH was abnormally high while his total serum T4, T3, and free T4, T3 were within normal limits, except for slightly low free T4 level at 7 months. The raised serum TSH decreased spontaneously to within normal limits after he was 9 months old.

With the recent development of techniques for testing thyroid activity, some interesting neonatal cases of thyroid dysfunction have been found. One of the most important developments in this field has been the introduction of mass screening for neonatal hypothyroidism, and several mass screening programmes have been reported. We have developed a new 'paired TSH assay method' (Miyai *et al.*, 1978). We were able to screen 91 400 babies between November 1975 and September 1978, and found 9 cases of primary hypothyroidism. We also found a boy who had high TSH but normal levels of thyroid hormones in the serum for 7 months, but whose TSH level decreased spontaneously to within normal limits after 9 months. This syndrome, which apparently differs from the transient neonatal hypothyroidism reported by La Franchi *et al.* (1977) and Delange *et al.* (1978), is described.

Case report

A baby boy was born after a normal pregnancy of 42 weeks without any complications or medications. Delivery was induced by aspiration, but vital signs of the baby were normal and the Apgar score was 10. At birth he weighed 3470 g and was 51·5 cm long. He had none of the normal signs of congenital hypothyroidism—such as, respiratory distress, hypothermia, peripheral cyanosis, hypoactivity, poor feeding, abdominal distention, vomiting, oedema, or prolonged icterus. His 33-year-old mother had 2 other children; both were girls, one was aged 7 and the other 5 years. The serum thyroid stimulating hormone (TSH), total thyroxine (T4), and total 3, 5, 3′-triiodothyronine (T3) were determined by double antibody radioimmunoassay and free T4 and T3 were determined by equilibrium dialysis. These results in the parents and siblings were within normal limits. By our mass screening test for neonatal hypothyroidism, the TSH in the patient's dried blood specimen was estimated as about 50 μU/ml, which is higher than the cut off point, and so he was again examined at 2 months. He was a well nourished infant, with no signs or symptoms of congenital hypothyroidism such as a cold, dry, mottled skin, an enlarged tongue, a hoarse cry, constipation, or goitre. He had an umbilical hernia but this disappeared at 4 months. At 9 months, *x*-ray examinations showed that the bone age and sella turcica were normal. His height and weight increased normally to 77·5 cm and 10 kg at 15 months.

The results of thyroid function tests are summarised in the Table. From 1 to 7 months, the serum TSH levels of the patient were significantly higher than those of age-matched normal babies. On radioimmunoassay, serial dilutions of serum at 2 months gave a curve parallel to that for serial dilutions of standard TSH. The raised TSH decreased to the upper normal limits from 9 months, and the TSH response to an intravenous injection of thyrotropin releasing hormone (TRH) (10 μg/kg) was also normal at 9 months. The serum concentrations of total T4 and free T4 were within normal limits except for low levels of free T4 at 7 and 9 months. Total T3 and free T3 were within normal limits. Total reverse T3 (r-T3) concentrations were within normal limits. Thyroidal uptake of ^{131}I and the standard energy metabolic rate were normal after 9 months, and tests for antithyroid antibodies were negative.

Discussion

Up to 7 months of age, the serum TSH level of this patient was found to be high by radioimmunoassay. This high level was not caused by a nonspecific reaction in radioimmunoassay because values for serial dilutions of the serum gave a curve parallel to that obtained with serial dilutions of standard TSH. The biological activity of the raised TSH is unclear.

Even if total T4 is normal, the increased thyroxine-binding globulin may cause decrease in free T4, which is considered to be the physiologically active

Table *Thyroid function tests in a baby with transient hyperthyrotropinaemia*

	Serum concentration of hormones						
Age (*months*)	*TSH* (*μU/ml*)	*T4* (*μg/100 ml*)	*Free T4* (*ng/100 ml*)	*T3* (*ng/100 ml*)	*Free T3* (*ng/100 ml*)	*r-T3* (*ng/100 ml*)	*Other tests*
1	(50·0*)						
2	24·0	11·1	2·35	248	0·327	61·0	Anti-thyroglobulin <1:20 Anti-microsome <1:20
4·5	11·3	14·1	—	328	—	80·3	
7	29·5	9·5	2·04	269	0·323	—	
9	8·1	8·4	1·75	240	0·341	—	Standard energy metabolic rate + 0·5%
	after TRH						
	30 min 27·0						
	60 20·0						
	90 18·5						
	120 12·5						
11	4·5	12·1	3·43	193	0·322	—	^{131}I uptake 17·5%
15	7·7	12·0	2·76	210	0·328	58·2	
Normal range							
1–3	2·8–12·0	7·0–14·6	2·10–3·54	192–260	0·291–0·495	37–104	
4–6	1·4–10·6	7·0–13·4	2·42–3·26	133–329	0·214–0·522		
7–24	1·3– 7·3	6·8–16·8		131–271		20–103	
Adult	<1 – 7·4	4·8–11·0	1·66–3·38	100–200	0·124–0·396	31–81	

*Estimated by a screening test on a dried blood specimen

Conversion: traditional units to SI—thyroxine: 1 μg/100 ml ≈ 12·87 nmol/l, triiodothyronine: 1 ng/100 ml ≈ 0·01536 nmol/l.

form. In our patient, the free T4 level was normal or low when TSH was raised before 7 months of age, and was low or normal when TSH became normal after he was 9 months old. At 9 months the response of TSH to TRH was within normal limits although free T4 was low. This finding indicates that decrease in free T4 was unlikely to be the cause of the raised TSH. Another active thyroid hormone, T3, is also known to be low in some neonatal conditions (Cuestas *et al.*, 1976). Our patient, however, had normal levels of total T3 and free T3 and was clinically euthyroid.

Several syndromes of inappropriate secretion of TSH have been reported, including neoplastic production of TSH, low response of the pituitary or peripheral tissues, or both of these, to thyroid hormone, and abnormal stimulation of TSH (Gershengorn and Weintraub, 1975). Increased TSH in addition to raised thyroid hormones is a characteristic of these syndromes. It is unlikely that our patient with a 'normal' T4 level and 'transient' hyperthyrotropinaemia had any of these syndromes.

Similar transient hyperthyrotropinaemia in infants was reported by La Franchi *et al.* (1977), and Delange *et al.* (1978). The infants they described had low total T4 when TSH was raised, and they called this syndrome 'transient neonatal hypothyroidism'. Our patient, however, had a normal total serum T4 level. Furthermore, his hyperthyrotropinaemia lasted for 7 months whereas in their patients it lasted only 2–6 weeks. Four of 6 cases reported by Delange *et al.* (1978) were in premature babies, but our patient was born at term. Therefore, this case dose not seem to be a case of transient neonatal hypothyroidism.

Oddie *et al.* (1977) reported that the progressive decrease in serum TSH and the increase in serum T4/TSH ratio in infants of 35 to 45 weeks' gestation is compatible with a progressive increase in feedback sensitivity to suppression of TSH release by thyroid hormone. Probably in this case slight immaturity in the responsiveness of the pituitary gland or of the peripheral tisssue or thyroid gland, or both, resulted in transient hyperthyrotropinaemia which maintained normal levels of serum thyroid hormones.

For effective treatment of congenital hypothyroidism, administration of thyroid hormones should be started as soon as possible. But we recommend that no treatment should be given in patients with high TSH but normal thyroid hormone levels, such as our patient.

This work was supported in part by grants from the Ministry of Health and Welfare and the Ministry of Education of Japan. We are grateful to Dr K. Kawabata for permission to study his patient, to Mr M. Kawashima for his technical help, to Dr and Mrs A. Ichihara for their valuable advice in preparing the manuscript in English, and to Mrs T. Wada and Miss M. Kawai for their secretarial assistance.

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British Paediatric Association

Proceedings of the Fifty-first Annual Meeting

The Annual Meeting of the British Paediatric Association was held at York from 27–31 March 1979. 410 members attended together with 3 Heinz Fellows, Observers from the Department of Health and Social Security, and the Scottish Home and Health Department, and 226 guests. The George Frederic Still Memorial Lecture was given by Prof. R. J. Haggerty (Harvard School of Public Health). Three speakers from developing countries gave lectures at a session on Deprivation organised to commemorate the International Year of the Child.

The Annual General Meeting of the British Paediatric Association was held on Thursday, 29 March 1979. The President, Prof. O. H. Wolff, was in the chair.

The minutes of the last meeting, which had been published in the *Archives of Disease in Childhood*, were received and approved.

ELECTION OF OFFICERS. The following were elected.

PRESIDENT:	Dr G. M. Komrower
HONORARY SECRETARY:	Dr D. R. Harvey
HONORARY ASSISTANT SECRETARY:	Dr C. H. Nourse

MEMBERS OF COUNCIL 1979–82: Dr D. P. Addy, Dr J. D. Andrew, Prof. F. Cockburn, Dr B. W. Lewis, Dr L. Rosenbloom, Dr H. B. Valman, Dr S. G. F. Wilson.

HONORARY MEMBERS: Prof. H. Ali Khan, Dr N. Kretchmer, Dr R. Whitehead.

MEMBERS: C. J. Bacon (Northallerton), S. E. Barnes (Salisbury), N. R. Belton (Edinburgh), J. W. T. Benson (Liverpool), D. Bentley (London), I. Blumenthal (Bradford), J. G. Bissenden (Birmingham), R. L. Broadhead (Manchester), D. S. K. Brookfield (Southampton), L. P. Carroll (Leicester), D. J. Carson (Craigavon), I. Chalmers (Oxford), P. Congdon (Leeds), K. D. Connolly (Ballinasloe), Jennifer M. Cowen (Liverpool), J. G. Davies (Birmingham), Blanche M. Dawson (Aberdeen), Ruth E. Day (Glasgow), B. Denham (Dublin), J. F. Dossetor (Glasgow), E. J. Eastham (Newcastle), D. R. Evans (Cardiff), P. J. Fleming (Bristol), Sally E. Flew (Hounslow), Patricia Franklyn (Bradford), Eva A. Frommer (London), D. C. Gordon-Nesbitt (Manchester), Elizabeth Griffin (Dublin), D. Hall (London), C. P. Hallett (Bury), Katherine A. Hallidie-Smith (London), O. J. Hanmer (Aberdeen), R. F. Harris (Wegberg), J. Z. Heckmatt (Leeds), G. M. A. Hendry (Edinburgh), Elaine M. Hicks (Belfast), Marion Hommers (Coventry), I. A. Hughes (Cardiff), J. C. Hyde (London), Susan J. Ilett (Sheffield), J. G. Jenkins (Belfast), R. F. Joanes (Stourbridge), R. Leanage (London), R. J. Levinsky (London), J. MacKinnon (London), P. Manuel (London), Carol P. Millns (Lincoln), I. Mitchell (Airdrie), C. J. Morley (Manchester), Anne Murphy (Louth), C. S. Nelson (Glasgow), J. H. Nirmal (Hartlepool), A. Oakhill (Birmingham), J. P. Osborne (Bristol), G. G. Owens (Liverpool), Barbara Phillips (Manchester), L. Polnay (Nottingham), F. N. Porter (Aberdeen), C. J. Rolles (Southampton), M. Joyce Rubissow (Birmingham), N. Rutter (Nottingham), O. Smales (Nottingham), M. L. Smith (Derby), Olga Stark (London), Ann L. Stewart (London), J. K. Stothers (London), I. L. Swann (Cardiff), Joan M. Tarnoky (Reading), Vivian V. Tracey (Northampton), R. S. Trompeter (London), Shelagh Tyrrell (London), J. Wagget (Newcastle), J. G. Watson (London), R. W. Watt (Wigan), Marjorie E. Watts (London), A. R. Wilkinson (Oxford), M. J. H. Williams (London), M. L. N. Willoughby (Glasgow), Vanessa M. Wright (London), T. D. Yuille (Bristol).

Report of the Council 1978–79

1. OBITUARIES

The Association has suffered the loss of Dr L. O. Abeyaratne, Prof. R. Debré (Honorary Members), Dr C. K. J. Hamilton (Original and Honorary Member), Prof. A. Holzel (Honorary Member), Dr R. J. Isaacs, Dr W. W. Payne (Honorary Member), Prof. H. Valquist (Honorary Member), and Dr H. Parry Williams.

2. DISTINCTIONS

Council has noted with great pleasure that Prof. F. S. W. Brimblecombe has been appointed first chairman of the Joint Committee for Children; Prof. S. D. M. Court has been awarded the Rosen von Rosenstein Medal for 1979; Dr D. Gairdner has been awarded the 1978 Dawson Williams Memorial Prize, Dr H. Jolly the Medical Journalists Award for 1978, and Dr E. M. Widdowson the CBE.

3. COUNCIL

Membership. The following members of the Association have served on Council during 1978–79: Prof. O. H. Wolff (President), Dr E. H. Back, Dr R. D. H. Boyd (Honorary Assistant Secretary), Dr C. G. D. Brook, Dr A. F. Conchie, Dr Barbara Davies, Dr W. Davies, Prof. E. E. Doyle, Dr D. W. Fielding, Dr C. A. S. Galloway, Dr J. R. Harper, Dr A. D. M. Jackson (Honorary Treasurer), Dr G. M. Komrower (President Elect), Dr Sheila Lewis, Dr M. M. Liberman (Honorary Assistant Secretary), Dr J. M. Littlewood, Prof. June K. Lloyd (Honorary Secretary), Dr D. Morris, Dr T. C. Noble, Dr C. H. Nourse (Honorary Assistant Secretary), Dr Aileen Redmond, Dr N. J. Royston, Dr R. A. Shanks, Dr M. J. Simpkiss, Dr H. Simpson, Dr P. E. Walker, Dr B. Wolman, Dr M. H. Bellman (Junior Representative), Prof. D. Hull (Chairman of the Academic Board).

Observers. The Association is grateful to the following for assistance and advice both at Council and in many other ways: Dr Margaret Bell (Scottish Home and Health Department), Prof. F. S. W. Brimblecombe (Member of the Central Health Services Council), Mr A. Jolleys (President of the British Association of Paediatric Surgeons), Prof. T. E. Oppé (Adviser in Child Health, DHSS), Dr Marie Richards (Welsh Office), and Dr Esther Simpson (Department of Health and Social Security).

Meetings. Council met on three occasions: 13 May and 14 October 1978, and 10 February 1979.

4. MATTERS CONCERNING THE ADMINISTRATION OF THE ASSOCIATION

The Association's permanent staff continues to comprise an Executive Secretary and three Assistant Secretaries. It was necessary to take on a temporary secretary for the two months before the 1979 Annual General Meeting to process the booking forms.

The Association would like to record its continuing debt of gratitude to the Institute of Child Health for portering and mailing services, and the use of duplicating facilities and rooms for meetings.

Academic Board. The 13th Annual Report of the Board has been received by Council.

5. AWARDS OF THE ASSOCIATION

James Spence Medal—Prof. Kenneth Cross.

Donald Paterson Prize—Dr R. J. Levinsky.

Heinz Fellowships for 1979–80—Dr M. B. Abdurrahman, Prof. Mrs M. M. Mehta, and Dr S. K. Sen (Fellowship A); Dr C. D. Moyes, Dr A. J. R. Waterston, and Dr R. J. West (Fellowship C). Council is continuingly grateful to H. J. Heinz and Company for their valuable support. The Association remains indebted to the Nuffield Foundation for their advice and administrative help.

6. FINANCE AND ALLIED MATTERS

The Directors of Unigate have again generously donated their annual travel grant of £225 and have supplied the programme and all stationery for the 1979 Annual General Meeting.

The BPA continues to benefit by a share of the profits from the sale of the *Archives of Disease in Childhood*.

7. MEETINGS OF THE ASSOCIATION

The 50th anniversary meeting of the Association was held at York in April 1978. 639 members and guests attended. A special anniversary meeting and dinner was held in London on 7 July 1978. 168 members and guests attended.

Council wishes to record its appreciation to the Academic Board in organising the scientific programme for these meetings and to thank the many members and guests who submitted papers. Council also wishes to thank the conveners and members of specialty groups (12 of which held sessions during the meeting) for their contributions.

The next Annual Meeting of the Association will be held from 15–19 April 1980.

8. STANDING COMMITTEES AND WORKING PARTIES OF THE ASSOCIATION

Reports have been received by Council, and comments have been submitted to government departments and other bodies on many important issues.

This has been a particularly busy year for the Association and Council is deeply grateful to the members who served on committees and working parties and also to those who represented the Association on both statutory and voluntary bodies. Many individual members have helped the Association by their advice, suggestions, and criticisms.

Council wishes to record its special appreciation of the work of the Editors of the *Archives of Disease in Childhood*; the journal continues to be of the greatest value to British paediatrics.

Other agenda items

1. Dr C. H. M. Walker outlined the work of the BPA Health Statistics Sub-committee during 1978 both in the preparation of the BPA *International Classification of Diseases* and its involvement with the Child Health Computing Committee of the DHSS currently investigating methods of medical data storage.
2. The meeting approved the establishment of a category of Associate Membership for Senior Clinical Medical Officers and Clinical Medical Officers whose work is mainly in the field of child health.

SCIENTIFIC PROCEEDINGS

GEORGE FREDERIC STILL LECTURE. The lecture was delivered by Prof. R. J. Haggerty, Roger Irving Lee Professor of Public Health, Harvard School of Public Health, Boston, on 'Life stress, social support, and health'.

National Childhood Encephalopathy Study—a preliminary report. M. H. Bellman, D. L. Miller, P. D. Poore, and E. M. Ross. London.

The National Childhood Encephalopathy Study seeks to assess the relative risk of serious neurological disorders, associated with immunisation, in young children. It also attempts to identify other factors that may cause or predispose to the development of such disorders in immunised and unimmunised children.

A case control analysis was carried out on children between ages 2 months and 3 years admitted to hospital with a defined group of clinical conditions.

In the first year 258 cases were identified. The most common diagnoses were febrile convulsions (34%), encephalitis (26%), and infantile spasms (15%). There was no constant aetiological pattern and in only 10 (4%) cases was the cause clear. The sex ratio was approximately equal, and the age distribution shows a peak at 6 months, with a gradual decline during the next 2½ years. Comparing cases with controls there was no significant difference in the proportion of children immunised within the period of 28 days before admission.

Preliminary results have not identified a significant association between encephalopathy in children and recent immunisation. Although a clinical diagnosis can often be made, there remains a group of children in whom the causal factors and classification of neurological disorder is obscure.

A study of heart rate and rhythm in normal schoolchildren. P. G. B. Johnston, F. Johnston, J. M. Richards, E. A. Shinebourne, and D. P. Southall. Dorchester.

Cardiac arrhythmias associated with sinus node dysfunction have been suggested as a cause of fits, faints, and 'funny turns' in childhood. However information on normal heart rate and rhythm is poorly documented and therefore single 24-hour ECG recordings were performed on 90 randomly selected healthy 7- to 11-year-old children. The mean highest heart rate over 9 beats was 164±16, the mean lowest heart rates were 49±6 over 3 beats and 56±6 over 9 beats' duration. At their lowest heart rates 42 (46%) had intermittent junctional rhythms. One child had episodes of complete 2:1 and Wenckebach A–V nodal block and 7 had intermittent prolongation of the PR interval (>0·20 seconds). 19 had isolated atrial premature beats. In a randomly selected subgroup of 29 children, 23 (79%) had sinoatrial Wenckebach block and 5 (17%) had 2:1 sinoatrial block patterns.

A history and clinical examination was taken on all children studied and this showed no correlation between variations in rhythm and rate and clinical findings. This study demonstrates that normal children exhibit variations in heart rate and rhythm hitherto considered to be abnormal, and therefore normal data must be carefully considered before making a diagnosis of conducting system disorders such as the sick sinus syndrome.

A follow up study of disturbed 3-year olds. P. J. Graham, N. Richman, and J. Stevenson. London.

A total population of 3-year-old children were screened for behaviour disturbance using a standardised procedure of known reliability and validity. Approximately 100 children were identified as showing significant problems and these were matched by sex and social class with a similar number of control children. These children were followed up at 4 and 8 years. Over 90% of the mothers were interviewed at 8 years.

There was a considerable amount of continuity. At 8 years 62% of the 3-year problem group were still disturbed compared with 22% of the controls—a highly significant difference. Independent ratings made by fathers and teachers confirmed that continuity was not merely a function of the mother's perception of the child as disturbed. Family relationships and maternal mental health at 3 years were not good predictors of behavioural outcome at 8 years. Few of the disturbed 8-year olds had been in receipt of any form of professional service.

Findings were discussed in relation to prediction and possible preventive measures for, despite the high level of continuity, only about one-third of disturbed 8-year olds would have been identified on the basis of disturbance at 3 years.

Longitudinal study of overweight children and young adults in the national survey of health and development. O. Stark, E. Atkins, and O. H. Wolff. London.

From the original population of 13 687 children born in one week in March 1946 a cohort of 5362 has been followed at regular intervals. Weights and heights are available at ages 2, 4, 6, 7, 11, 15, 20, and 26 years. A power-type index of weight for height, age, and sex was used as a 'standard' for calculation of percentage overweight and underweight. The prevalence of overweight (defined as $>20\%$ above standard) was 1·6 and 2·8% for males and females respectively at 6 years; 2·0 and 3·7% at 7 years; 6·7 and 9·6% at 11 years; 6·6 and 9·6% at 14½ years; 5·3 and 6·6% at 20 years; and 12·8 and 11·5% at 26 years. Three-quarters of girls and nearly half the boys who were overweight at 6 years were overweight at 26 years and various patterns were noted in the evolution of overweight from childhood to adulthood. In general the risk of being overweight in adulthood increased with the degree of overweight present in childhood. The degree of overweight changed gradually with time so that it exhibited greater stability in the short term than over longer periods.

The correlation between relative weight status in adult life and childhood increases as the child gets older; thus only 10% of the overweight 26-year-old women had been overweight at age 6 years, and this percentage rises to 45% at 14½ years. The corresponding percentages for men are 6 and 28%.

Effects of supplementary vitamin D during pregnancy on Asian women and their infants. O. G. Brooke, C. Bone, I. R. F. Brown, N. D. Carter, D. Maxwell, and V. Robinson. London.

Pregnant Asian women have lower blood levels of vitamin D than Europeans (Dent and Smith, 1969) and their infants are prone to hypocalcaemia (Watney, 1975) and neonatal rickets (Ford *et al.*, 1973). We therefore investigated the effect of vitamin D supplements during pregnancy in a group of Asian women and their infants. Ergocalciferol, 1000 IU/day, or placebo were given by random allocation to 61 Asians during the last trimester. The trial was double blind. Blood calcium, phosphate, alkaline phosphatase, 25-hydroxycholecalciferol (25-OHD), and vitamin D binding globulin (VDBG) were measured on entry to the trial, after delivery, and in cord blood. Infant blood calcium was measured on day 3 and 6, and fetal growth was assessed by anthropometry. The following results were obtained. (1) Mean plasma 25-OHD declined in late pregnancy in the control group and was very low in cord and postpartum blood (9 and 12 nmol/l respectively). (2) The treated group had significantly higher mean plasma 25-OHD in cord and postpartum blood (110 and 153 nmol/l). (3) There was a positive correlation between maternal and cord blood 25-OHD ($r=0{\cdot}92$, $P<0{\cdot}001$). (4) Alkaline phosphatase levels were lower in the treated than the control group, both in maternal and cord blood ($P<0{\cdot}05$). (5) There was no difference between treated and control groups in fetal growth, neonatal calcium levels, or maternal and infant VDBG levels.

We conclude that, while vitamin D supplements may be necessary in Asians to prevent deficiency during pregnancy, they do not influence fetal growth or neonatal calcium levels.

References

Dent, C. E., and Smith, R. (1969). Nutritional osteomalacia. *Quarterly Journal of Medicine*, **38**, 195–209.

Ford, J. A., Davidson, D. C., McIntosh, W. B., Fyfe, W. M., and Dunnigan, M. G. (1973). Neonatal rickets in Asian immigrant population. *British Medical Journal*, **3**, 211–212.

Watney, P. J. M. (1975). Maternal factors in the aetiology of neonatal hypocalcaemia. *Postgraduate Medical Journal*, **51**, Supplement 3, 14–17.

What can be expected from growth hormone therapy? W. Hamilton. Glasgow.

The clearance rate of administered human growth hormone (hGH(UK)) was studied in 12 children who were receiving hGH(UK) for short stature due to isolated growth hormone deficiency.

Administration of hGH stimulates a rise in plasma cortisol, and gives an 'effective' plasma level of hGH from 2·5 to 6 h postinjection. The high level of plasma oestradiol suggests that administered hGH (or an impurity) stimulates ovarian function. Likewise the levels of T3 and T4 with a normal TSH level suggests possible chronic thyroid stimulation from the hGH.

These findings stimulated an analysis of the clinical data on 29 children treated with hGH for short stature over 2 to 4 years. Only 2 boys out of 20 crossed the 3rd centile upwards; 18 did not increase significantly their growth velocity. When height was charted in relation to bone age, bone age accelerated faster than increments in height were obtained. Similar findings were observed in 9 girls (charts available).

These data suggest that hGH (or an impurity) accelerates osseous maturation, either via thyroid or gonadal stimulation, to a greater degree than it increases linear growth.

The physical, biochemical, and immunological status of hGH(UK) was therefore defined. The conclusions are that hGH(UK) contains up to 50% polymer (likely to reduce total growth stimulating effects) and a measurable amount of both LH and FSH (stimulants of gonadal activity). The net effects predictable therefore are early osseous fusion (from gonadal stimulation) and a restriction in the rate of linear growth (only 50% of the dose administered effective). Thus it can be expected that ultimate short stature (in most cases less than 3rd centile) is likely to result from the treatment of patients with short stature with hGH(UK).

Temperature control in incubators. J. K. Stothers and K. W. Cross. London.

Abdominal skin temperature is commonly used to govern the environmental temperature in servo-controlled incubators. Ill babies are frequently nursed prone, thus insulating the abdomen, rendering it thermally unresponsive to external temperature change and unrepresentative of general surface temperature which governs sensory input and response.

It therefore seemed desirable to find a site responsive to environmental temperature change and representative of mean skin temperature. Both thermographic (Clark *et al.*, 1978) and thermocouple measuring systems were used. The infants were nursed prone in a Vickers incubator (model 79) while temperatures were recorded at 9 sites using the thermocouple thermometer. When possible, infrared thermograms were filmed simultaneously.

Both methods gave similar values of mean skin temperatures, and the upper arm and thigh were found to approximate closely to the mean. In addition, they responded well to environmental temperature changes.

These findings suggest that if incubators are to be used in the servo mode, and this is in itself questionable, the above sites would be more suitable for sensor placement than the insulated abdominal skin of the prone infant.

Reference

Clark, R. P., Cross, K. W., Goff, M. R., Mullan, B. J., Stothers, J. K., and Warner, R. M. (1978). Neonatal whole-body thermography. *Journal of Physiology*, **280**, 2P–3P.

Early diagnosis of group B streptococcal disease in the newborn.•M. J. Lewins and J. Dodge. Cardiff.

A review of 14 infants admitted to the neonatal intensive care unit of the Hospital for Sick Children, Toronto, with early group B streptococcal (GBS) disease demonstrated the difficulty of establishing a clinical diagnosis from the history, examination, and chest *x*-ray. All infants were initially diagnosed as having respiratory distress syndrome (RDS).

Nine of these infants died. All infants who had apnoeic episodes before antibiotic therapy died. Those infants who survived received antibiotics at a significantly earlier age but were otherwise similar to the group who died.

In a subsequent prospective study, all infants admitted with a provisional diagnosis of RDS had their gastric contents aspirated and the aspirate subjected to culture, Gram staining, and a 'shake test' for surfactant activity. All the infants also had blood cultures and differential white cell counts. All received antibiotics. In this time 6 infants were identified as having GBS within an hour of admission. Four of these infants survived.

It is concluded that these methods offer the opportunity for early clinical diagnosis of GBS and, with early antibiotic therapy, may reduce mortality from the disease.

Prevention of thalassaemia major by antenatal diagnosis. B. Modell, M. A. Angastiniotis, D. V. I. Fairweather, M. Matzabio, and R. H. T. Ward. London.

Prevention of thalassaemia major by antenatal diagnosis, using fetal blood samples obtained at 18–22 weeks' gestation, is now an established procedure: 170 cases have been managed at UCH. There are 2 methods for fetal blood sampling: blind needling of the placenta carries a 7% risk of immediate intrauterine death, while fetoscopy, with fetal blood sampling, appears to carry a 15–20% risk of premature labour with its attendant problems. There is an approximately 1% risk of laboratory misdiagnosis—that is, confusion between thalassaemia major and thalassaemia trait. As married couples at risk for thalassaemia major infants can be detected before they have had an affected child, such couples should now be sought in the antenatal clinic (and possibly before they reach this stage), so that they can receive genetic counselling and consider the offer of antenatal diagnosis. The response of at-risk couples to this offer differs widely between the two affected communities in Britain. Nearly 100% of Cypriots request antenatal diagnosis, while about

60% of Indian/Pakistani couples do so. This cultural contrast gives some guidance about the most desirable methods of screening populations for carriers. This work has wider implications in that it provides a small-scale model for the attitudes and requirements of the British population when antenatal diagnosis for endemic common inherited diseases, such as fibrocystic disease and phenylketonuria becomes available, as is likely in the next few years.

Problems of antenatal screening of a total population for neural tube malformations. K. M. Laurence, K. Evans, B. Hibbard, and C. J. Roberts. Cardiff.

Although the collaborative survey shows that prenatal detection using serum alphafeto protein estimated at 16–18 weeks is feasible, the problems of introducing and conducting a population screening programme have not been identified. A screening programme was set up, based on all the pregnancies in mid-Glamorgan from 1977 to investigate the problem. The following comments are based on the first 3330 completed pregnancies by the end of the first 6 months.

Successful population screening depends on a good laboratory, genetic counselling, transport, communication and co-operation with staff, and compliance of the mothers. An efficient supra-regional radioimmunoassay laboratory is essential. Genetic counselling services have to cope not only with preamniocentesis and pre- and postabortion counselling, but also with the other problems coming to light during screening. Efficient transport of specimens to the laboratory and reports back to the clinics and consultants is essential. Communication between clinics, laboratory, obstetricians, GPs, genetic clinics, etc., is vital. Good compliance of patients' understanding the aims of screening, attending early enough for this to be instituted, and GPs being co-operative and referring early enough to the clinic, is one key to success. An efficient ultrasound to date pregnancies accurately and competent amniocentesis with few sequential abortions are essential. With serum samples taken between 16 and 18 weeks, amniocentesis tends to be carried out when discrimination between normal and abnormal AFP values become blurred. This leads to possible problems of both false-positive and negative. Obstetricians sometimes deviate from usual procedures which may also lead to tragedy.

Well conducted screening can reduce the number of babies with neural tube malformations reaching term to less than 10%, leading to a considerable saving of paediatric resources and prevention of much family anguish.

Diagnosis of vesico-ureteric reflux without bladder catheterisation. S. T. Meller, H. B. Eckstein, and B. C. H. Ward. Carshalton.

The method of indirect radionuclide cystography (RNC) is described. The urinary tract is imaged with a gamma camera after intravenous administration of a technetium-labelled chelate. When the bladder is full the child is required to void on request. Reflux which reaches the renal pelvis will generally be recognised from the analogue gamma camera images. Using a small computer to store digital images and to generate time/activity curves from the kidneys and bladder improves the diagnostic accuracy. Spontaneous reflux during bladder filling may also be recognised.

25 children, aged 3 to 12 years, first had standard radiological investigation—an intravenous urogram and micturating cystourethrogram (MCU)—and were then referred for RNC. They were examined by one observer without prior knowledge of the radiological findings. Six children were unable to void on request. Three studies were spoiled by movement artefact. In 14 examinations (23 normal units and 5 refluxing units) the MCU and RNC proved to be in accord. In 2 cases there were conflicting results.

The RNC avoids the trauma of bladder catheterisation and provides a physiological approach to the diagnosis of reflux. The radiation exposure is significantly reduced. We recommend the use of this technique in selected cases.

Renal growth following unilateral antireflux surgery. J. D. Atwell and P. Cox. Southampton.

112 children treated surgically for unilateral vesicoureteric reflux at the Wessex Regional Centre between 1969 and 1975 were reviewed. The ages of the patients ranged from one month to 13 years and the mean length of follow-up was 3 years 11 months. Renal growth was assessed in each patient by measurements of renal length from serial intravenous pyelograms performed preoperatively and at intervals during the period of follow up.

Calculations of the mean renal lengths preoperatively and at 3 months, 1 year, and 5 years postoperatively suggest that renal growth accelerates after successful reimplantation of the ureter. The phase of rapid renal growth was confined to the first postoperative year and is greatest in the first 3 months after antireflux surgery and was equal in both kidneys. The mechanisms accounting for these alterations in renal growth remain obscure.

Adhesion of Enterobacteriaceae to buccal epithelial cells.

D. Candy, J. T. Harries, T. S. M. Leung, W. C. Marshall, and A. Phillips. London.

The pathophysiology of infantile diarrhoea is currently under intense investigation particularly in relation to adhesion of bacteria to the alimentary tract, which we have studied using human buccal epithelial cells (BEC).

A pathogenic strain of *Escherichia coli* (O26:K60) known to adhere to human fetal intestine (McNeish *et al.*, 1975) adhered to adult BEC, while a nonpathogenic, nonadhesive strain (O1:K1) did not. Adhesion was temperature-dependent, correlated with fimbriae production, and was inhibited by breast milk. Serotypable *E. coli* from stools of 7 infants with acute diarrhoea, and *E. coli, Enterobacter* sp., *Proteus* sp. (and *Candida albicans*) from the small intestine of 3 infants with protracted diarrhoea, adhered to BEC from 6/7 and 3/3 of the infants' BEC respectively. The nonadhesive *E. coli* (O1:K1) adhered to BEC from the latter group. Adhesion of all *Enterobacteriaceae* was inhibited by D-mannose.

Our results indicate that BEC provide a simple model for studying intestinal adhesion of bacteria in man, and suggest that adhesion may be mediated by mannose-like receptors. Moreover, the test system has the important advantage that bacteria can be studied with cells from affected cases, and thus may provide a means of assessing the 'enteropathogenicity' of bacteria in individual patients.

Reference

McNeish, A. S., Turner, P., Fleming, J., and Evans, N. (1975). Mucosal adherence of human enteropathogenic *Escherichia coli. Lancet*, 2, 946–948.

A spoonful of sugar helps the medicine go down.

I. F. Roberts and G. Roberts. London.

The aim of this study was to see if chronic administration of liquid medicines sweetened with sucrose had a deleterious effect on children's teeth. The teeth of a group of 44 children aged less than 6 years who had been taking syrup medicines regularly for at least 6 months were compared with those of a control group of 47 children of similar ages. Dental decay was assessed, using established dental formulae, by measuring their carious index, plaque index, and gingival index. The dentist's ability to be consistent in his measurement of dental decay was checked by performing repeatability tests; analysis of these using the Spearman's rank correlation coefficient indicated that the clinical findings were sufficiently reliable for the purpose of this study. A questionnaire, related to other factors known to children's deciduous teeth was completed at the end of each dental examination.

The children who received sucrose-based medicine had more carious teeth ($P<0{\cdot}05$) and more gingivitis ($P<0{\cdot}05$, Mann-Whitney U test). Information obtained from the questionnaire was analysed using the χ^2 test, and showed no difference between the two groups for cariogenic factors unrelated to medicines.

It is concluded that sucrose-based medicine regularly administered to children for 6 months cause dental caries and gingivitis. Liquid medicines for children should therefore be either unsweetened or sweetened with noncariogenic substances.

A comparison of intellectual abilities following treatment for leukaemia and solid tumours during childhood.

C. Eiser. London. To be published in full in the *Archives*, 1980, **55.**

Bone marrow relapse on treatment in childhood acute lymphoblastic leukaemia.

J. James, J. H. Baumer, B. Howlett, P. J. Kearney, and M. G. Mott. Bristol.

A retrospective study was carried out on children with acute lymphoblastic leukaemia having their first relapse in the bone marrow while on treatment. Among 190 children from 9 major centres in the United Kingdom, there were no long-term survivors. The median durations of complete and haematological remission were 80 and 97 days respectively. The risk of developing meningeal leukaemia in the second remission was 46·1% and for overt testicular infiltration in boys was 15·7%. The main factor at diagnosis affecting outcome was the initial total white blood count. Children with a high white count relapsed earlier while on treatment and survived for a shorter period of time after relapse, with shorter duration of the second remission. They achieved a second remission as readily as children with low initial white blood counts. These effects appeared to be dependent on the T-cell status of the leukaemia.

There was a group of children in whom a first remission was achieved only with difficulty, who were particularly resistant to treatment after relapse. The majority of children who attained a second remission did so within 12 weeks of relapse. There were a few children who survived for periods up to one year in relapse, however. Children who had not received vincristine and prednisolone as maintenance therapy before relapse were more likely to achieve a second remission. Those children who were resistant to the more commonly used drugs also appeared to be resistant to other groups of drugs. We conclude that children who end their first remission with relapse in their bone marrow while still receiving treatment are not curable by present chemotherapeutic regimens. Any attempt at improving this situation (for example, by bone marrow transplant) will need to take account of the high risk of CNS leukaemia subsequently developing in these children.

A special session on Deprivation was organised to commemorate the International Year of the Child

Deprivation in London: social and economic factors. N. D. Deakin.
Individual differences and protective factors in children's responses to deprivation. M. L. Rutter.
Child growth, malnutrition, and deprivation. L. Mata.
Family size and deprivation in the UK. D. Greaves.
Identifying community resources and using them—rural Maharashtra; some interventions. R. S. Arole.

British Paediatric Tropical Child Health and Community Paediatric Groups—Combined Session.

Organisation of rural maternal and child health services in Tanzania. W. Madundo.
A profile of infant growth and health in inner city deprivation. J. P. Stanfield.
Problems and strategies in the management of deprivation in preschool children. J. W. Partridge.
The changing pattern of infant deaths in Sheffield 1968–77. R. Sunderland.
Volume and composition determination of suckled breast milk. A. Lucas.
Amenorrhoea in the deprivation syndrome. D. MacCarthy.

POSTER PRESENTATIONS

Errors in the diagnosis of child abuse. M. W. Arthurton and M. F. G. Buchanan.

Diarrhoea and measles in Tanzanian children. D. S. K. Brookfield, E. J. Bell, B. P. Gosgrove, and C. R. Madeley.

Pattern of jaundice in term infants over a 5-year period. K. Costeloe, J. D. Baum, and D. Hill.

When should babies be sent home from SCBUs? D. P. Davies, V. Haxby, and A. S. McNeish.

Age-dependent changes in lymphatic response during the neonatal period. E. J. Guiney, P. Blake, O. Browne, O. Hensey, N. O'Brien, P. Puri, and D. J. Reen.

Congenital complete heart block in the newborn associated with maternal systemic lupus erythematosus and other connective tissue disorders. J. D. Hardy, G. S. Banwell, R. Beach, F. Howard, S. Solomon, and V. Wright. Published in full in the *Archives*, 1979, **54**, 7–13.

Plasma 25 hydroxy vitamin D in pregnant Asian mothers and their babies. J. Z. Heckmatt, A. E. J. Davies, J. McMurray, and M. Peacock.

'Anaemia' with a 'normal' haemoglobin concentration: iron deficiency in cyanotic congenital heart disease. B. M. Holland, R. D. Hutton, C. Scott, A. Veale, and C. A. J. Wardrop.

Salt and sugar measure in the management of diarrhoea. P. Hutchins, J. Broomhall, and D. Morley.

Vitamin E and growth in the low birthweight neonate. M. I. Levene.

Drug use in preterm and term babies. T. A. Moreland and G. W. Rylance.

Stature and the family. C. D. Moyes.

Nine years old in London. M. Pollak.

Assessment of the short-term results of bile-drainage operations in extrahepatic biliary atresia (EHBA). H. T. Psacharopoulos, E. R. Howard, and A. P. Mowat.

Child Development Centre data: collection and usage. R. E. Pugh and L. Rosenbloom.

Origins of childhood handicap. M. Radford and C. E. M. Jones.

Drug availability and dosage information for children. G. W. Rylance.

Intubation practice in maternity hospital. R. H. Schwartz, J. D. Baum, and R. M. Gardiner.

Child health records and the computer. C. H. M. Walker and the BPA Health Statistics Sub-committee.

What causes kwashiorkor in the older child? A. J. R. Waterston.

Transpyloric feeding in very low birthweight infants. M. F. Whitfield.

Ultraviolet light and vitamin D status in epileptic children. M. Davie, J. L. Barnes, N. D. Barnes, and G. E. Roberts.

GROUP SESSIONS

British Paediatric Cardiology Section

Dopamine infusion—improved therapy for persistent transitional circulation. G. I. Fiddler.

A new approach to the treatment of transposition of the great arteries. R. C. Radley-Smith.
Exercise studies in children with transposition of the great arteries after Mustard operation. P. Weller.
Congenital heart disease and parental consanguinity in Asians. A. R. Gathrad.
Aortopulmonary window and associated anomalies: diagnosis and management. K. C. Lau.
Management and result of surgery in symptomatic infants with coarctation of the aorta. Susanna M. Hart.
Intracardiac electrophysiological studies in the assessment and management of cardiac arrhythmias in children. P. V. L. Curry.

British Paediatric Immunology Group

Four families with immunodeficiency and chromosome abnormalities. D. Candy.
Effects of sera from children with Crohn's disease on lymphocyte transformation *in vitro*. P. Hindocha.
Exudative response to milk and other proteins. Lynn Alexander.
Malnutrition, antibodies, and parasitic infestation in the tropics. F. Carswell.
A successful graft from an unrelated donor into an infant with SCID disease. K. Hugh Jones.
Purine studies in an infant with adenosine deaminase deficient severe combined immune deficiency. J. G. Watson.
Immunodeficiency secondary to enteropathic disorders. P. Hindocha.
Delayed separation of the cord and defective neutrophil mobility. Mary C. Greenwood.
Immunological aspects of appendicitis and abdominal pain in children. N. V. Doraiswamy.
A bacteriocidal polypeptide in amniotic fluid. C. M. M. Stern.

British Paediatric Neurology Association
Long-term outcome of some neurological diseases of childhood

Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA): prognosis and prevention. D. Gardner-Medwin.
Milestones on the downward path in the progressive degenerative brain diseases. E. M. Brett.
Childhood brain tumours—results of therapy and long-term problems. C. C. Bailey.
Long-term outcome of febrile convulsions. Sheila J. Wallace.
Basilar migraine in childhood. Judith M. Hockaday.
Opitz syndrome (hypertelorism hypospadias dull normal intelligence). N. J. O'Doherty.
Neuropathic bladder in spinal dysraphism. Malgorzata Borzyskowski.
Role of viruses in febrile convulsions. Helen Lewis. Published in full in the *Archives*, 1979, **54**, 869–876.
Metabolic effects of ketogenic diets in the treatment of children with epilepsy. Ruby Schwartz.
Carrier detection in Duchenne muscular dystrophy. J. R. Sibert. Published in full in the *Archives*, 1979, **54**, 534–537.

British Paediatric Nutrition, Metabolism, and Pharmacology Group

Biotin-responsive developmental deterioration and alopecia. L. S. Taitz.
Dietary treatment of 7 patients with homocytinuria treated from the newborn period. I. B. Sardharwalla.
Treatment of Hurler's disease (mucopolysaccharidosis IH: congenital α-iduronidase deficiency) by fibroblast transplant. Dorothy A. Gibbs.
Use of urinary lactate estimations in disorders associated with a lactic acidosis. D. B. Dunger.
Effect of the provision of school milk on the growth of schoolchildren. I. A. Baker.
Assessment of carbamazepine dose-frequency regimens in children. G. W. Rylance.
Salivary theophylline levels in the management of asthmatic children. S. M. Lena.
Naloxone kinetics in the newborn after IV and IM administration. T. A. Moreland.

British Society of Paediatric Endocrinology

Experience of screening for congenital hypothyroidism. J. A. Hulse.
A system for diagnosis of neonatal hypothyroidism. Sarah J. Bodden.
Screening for congenital hypothyroidism—does it have a place in the UK? N. D. Barnes.
Hormonal and auxologic patterns in boys with constitutional growth delay. J. L. Penfold.
Growth response to GH therapy in children with radiation-induced GH deficiency. S. M. Shalet.
Familial male pseudohermaphroditism due to 5α-reductase deficiency. M. O. Savage.
Prognosis of the Prader-Willi syndrome. B. M. Laurance.
Monitoring of serum prednisolone levels in patients with renal disease by solid phase radioimmunoassay (RIA). B. T. Rudd.
Congenital adrenal hyperplasia: are we detecting male salt losers? J. R. Sibert. To be published in full in the *Archives*, 1980, **55**.
A study of skeletal maturity in newly diagnosed juvenile diabetics. A. D. Edelsten.

Pancreatic polypeptide antibodies in diabetic children. D. I. Johnston.
Enteroglucagon: aspects of its developmental physiology. A. Lucas.
Seckel's syndrome—a case report describing its association with marrow hypoplasia and immune deficiency. R. R. Gordon.

British Paediatric Perinatal Group

Problem of persistent ductus arteriosus in the low birthweight infant. D. R. S. Smith.
Effects of raising abdominal pressure on rib cage distortion and the work of breathing in preterm infants. P. Fleming.
Psychosocial stress and onset of premature labour. R. W. Newton.
A study to determine normal fetal heart rate and rhythm: coincidentally highlighting failings in antepartum fetal heart rate monitors. Jean M. Richards.
24-hour tape recordings of ECG and respiration in the newborn infant with findings related to sudden death and unexplained brain damage in infancy. D. P. Southall. To be published in full in the *Archives*, 1980, **55**, 7–16.

Assessing standards of perinatal care

National uniformity in perinatal data collection: feasibility and desirability. I. Chalmers.
The Scottish perinatal mortality study. Gillian McIlwaine.
Lessons learned from a survey of newborn facilities in the south east region. H. R. Gamsu.
Open discussion on regional surveys of perinatal care.

British Paediatric Radiology Group

Polysynostoses (a group of skeletal dysplasias with possible inter-relationships). R. I. S. Gordon.
Copper deficiency syndrome. P. P. Franklyn.
Atlanto-axial joint in local and remote disease. G. M. Steiner.
Urinary tract stones in children. S. E. W. Smith.
Significance of the echo nephrogram. C. Metreweli.
Necrotising enterocolitis. J. Virgee.
Fine needle cholangiography. H. Carty.
Diagnostic problems in bowel malrotation in the neonate. G. M. A. Hendry.
Initiation of respiration and onward progress of bowel gas in the neonate. J. B. Fawcitt.
Evaluating speech problems. A. R. Chrispin.

British Association for Paediatric Nephrology

Kidney failure in children. C. Chantler.
Abnormalities of lymphocyte function in minimal change nephrotic syndrome and focal glomerular sclerosis. S. J. Chapman.
Steroid toxicity and the eyes in children with nephrotic syndrome. J. T. Brocklebank.
Differential glomerular cellularity in the nephrotic syndrome with minimal change or focal glomerular sclerosis. N. Yoshikawa.
Lupus nephritis in childhood and adolescents. M. C. Morris.
Inherited aldosterone deficiency. M. H. Winterborn.
Renal function after cardiopulmonary bypass surgery in children: the role of gentamicin. Susan Rigden.
Late metabolic acidosis: a reassessment of the definition. G. B. Haycock.
Effect of sterile vesico-ureteric reflux. Jean M. Smellie.
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Yeast opsonisation in children with chronic diarrhoeal states. D. C. A. Candy. To be published in full in the *Archives*, 1980, **55.**

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Chronic myeloid leukaemia in childhood. A. Heppleston.

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Cerebrospinal fluid methotrexate levels after high dose of intravenous infusion. A. Bosley.

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Archives of Disease in Childhood, 1979, **54**, 979–982

Neonatal Society

Meeting held on 29 June 1979 at the University of Glasgow

The female advantage in fetal lung maturation. M. E. Avery, J. S. Torday, H. C. Nielsen, M. Fencl, and R. V. Kotas. Department of Pediatrics, Harvard Medical School, Boston, and Tulsa, USA.

Male infants have a 1·7 times greater mortality rate from RDS than female ones. If the disorder is a reflection of immaturity with respect to pulmonary surfactant, then the lungs of female infants should be relatively more mature than those of male infants at a given gestational age. Naeye found that at between 25 and 32 weeks' gestation, female infant lungs were more mature by histological criteria (Naeye *et al.*, 1971). Further support for relatively greater maturity of female fetal lungs comes from an analysis of L/S ratios and cortisol in amniotic liquid from 167 pregnancies of 28–42 weeks, complicated and uncomplicated. At all stages of gestation, males had a lower L/S ratio than females. Lower cortisol levels were also noted in male infants. In an analysis of pressure-volume relationships in fetal rabbit lungs, the female fetuses retained more air at a given transpulmonary pressure than littermate males of 27 days' gestation, which is consistent with greater maturity. The response to glucocorticoid administration was also greater in the lungs of the female fetal rabbits. These observations support the hypothesis that the lung in the female fetus is more mature than that of the male.

Reference

Naeye, R. L., Burt, L. S., Wright, D. L., Blanc, W. A., and Tatter, D. (1971). Neonatal mortality, the male disadvantage. *Pediatrics*, **48**, 902–906.

Gut hormones in the neonate. T. E. Adrian, A. Aynsley-Green, S. R. Bloom, and A. Lucas. Department of Paediatrics, John Radcliffe Hospital, Oxford, and Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London.

Gut hormones exert important effects on gut growth, secretion, motility, and on intermediary metabolism, and may play a key role in the postnatal adaptations to enteral feeding. Using sensitive radioimmunoassays we have measured 10 entero-insular hormones in the plasmas of (a) 203 healthy term or preterm infants at birth or during the first 24 days of life, either before or at 30, 60, or 120 minutes after feeding, and (b) 10 6-day-old preterm neonates who had never been fed orally as they had hyaline membrane disease. Each infant contributed only one plasma sample, removed at the time of a routine clinical blood test. Basal levels of gastric inhibitory polypeptide (GIP), pancreatic polypeptide (PP), enteroglucagon (EG), neurotensin (NT), motilin, and gastrin all rose steeply during the neonatal period, reaching levels which exceeded those in healthy, fasting adults. In contrast, plasma concentrations of GIP, EG, NT, motilin, and gastrin did not show postnatal increases in the unfed group of infants. In addition, for 8 hormones (secretin, GIP, PP, NT, EG, motilin, gastrin, and insulin) we observed a progressive postnatal increase in the endocrine response to a feed. Profound changes occur therefore in gut hormone physiology after birth, and these changes may in part be due to enteral feeding itself. These data are relevant to the design of optimal feeding regimens for high-risk neonates.

The neonatal breast. J. McKiernan and D. Hull. Department of Child Health, Nottingham University.

A study has been made of breast development in the newborn infant. The diameter of the breast nodule was measured in 288 infants during the first 2 days of life. The values came within a normal distribution. In 149 male infants, mean birthweight 3·37 kg, the breast diameter was 7·54±0·25 (mean± SE), and in the 139 females, mean birthweight 3·19 kg, the breast diameter was 7·98±0·24 (mean±SE).

Breast size was also assessed in 115 low birthweight infants. In infants below expected body weight, 'small-for-dates' (SGA), the breast diameter was greater than that of infants of similar bodyweights but appropriate for gestational age (AGA).

The timing of onset of milk secretion by the neonatal breast has also been examined. Secretion began on the 6th to 8th day of life in 11 mature infants. Interestingly, of 13 SGA infants who were 'secretors', 11 were secreting on the 5th day or earlier. Delayed onset of secretion was noted in a small number of preterm, low birthweight infants. Some mature infants did not secrete milk.

Considerable breast engorgement, greatest in the 2nd and 3rd weeks of life, was found in healthy infants. There was a positive correlation between breast diameter on day 6 and plasma prolactin at this time ($R=0\cdot84$, $P<0\cdot001$).

The study of the neonatal breast and its secretions offers interesting insights into aspects of fetal and neonatal endocrinology and nutrition.

What do we know about resorption and conversion of vitamin D3 in premature infants? H. Wolf, G. Offermann, and V. Gräff (introduced by E. Widdowson). Department of Neonatology, Universität Giessen, and Department of Nephrology, Klinikum Steglitz, Freie Universität Berlin, West Germany.

The necessary supplementation of vitamin D3 is higher for premature infants than for term ones (1000 IU v. 500 IU a day). 1000 IU (25 μg) of vitamin D3 are equivalent to 9 μg or less of 25-(OH)-D_3 (Wolf *et al.*, 1975). Therefore the question arises whether resorption or conversion to 25-(OH)-D_3 is hampered in the premature infant.

Four groups of premature infants were observed during a 3- to 5-week period. In the control group (gestational ages 32 to 38 weeks) a vitamin D3-free formula (Meb-milupa) was given. The level of 25-(OH)-D_3 in plasma remained low (10 ng/ml; 25 nmol/l). The second group (GA 32 to 34 weeks) received 1000 IU vitamin D3 daily. The plasma level of 25-(OH)-D_3 rose to 25 ng/ml (62 nmol/l). The third group (GA 36 to 38 weeks) also received 1000 IU vitamin D3. This resulted in a 'calculated' level of 25-(OH)-D_3 up to 75 ng/ml (187 nmol/l) after 9 weeks. However, the same level was reached after only 3 weeks in a fourth group of infants of the same GA given 1000 IU vitamin D3 and small amounts of supplemental breast milk (up to 200 ml a day). These findings suggest that either resorption of vitamin D3 or its conversion to 25-(OH)-D_3 is diminished in the immature infant. Resorption may be enhanced by breast milk.

Reference

Wolf, H., Kerstan, B., and Kerstan, J. (1975). The requirements of vitamin D (cholecalciferol) and of 25-hydroxycholecalciferol (25-HCC) in premature children during their early life. *Klinische Paediatrie*, **187**, 331–341.

Ionised calcium in pregnancy. N. R. Belton, M. J. Forsyth, M. M. Giles, R. Elton, and J. O. Forfar. Department of Child Life and Health, University of Edinburgh, and Simpson Memorial Maternity Pavilion, Royal Infirmary, Edinburgh.

Vitamin D requirement during pregnancy has not been definitively established. Supplementary vitamin D (1000 IU a day), or a placebo, was given to two groups of pregnant women from the 12th week until delivery, and total Ca, ionised Ca, total protein, Mg, and P measured in plasma at 12 weeks, 24 weeks, 34 weeks, and delivery in both maternal venous blood and cord blood. Ionised Ca (mmol/l), measured using the Orion SS-20 analyser was (mean±SD and normal):

	Supplemented group	*Control group*
12 weeks (combined groups)	0·93±0·09 (45)	
24 weeks	0·89±0·08 (24)	0·91±0·08 (22)
34 weeks	0·87±0·11 (38)	0·87±0·09 (32)
Delivery	0·86±0·10 (7)	0·77±0·11 (11)
Maternal vein		
Unbilical vein	1·05±0·16 (8)	0·97±0·10 (11)
Umbilical artery	0·91±0·17 (7)	0·87±0·16 (8)

Thus ionised Ca decreased during pregnancy (difference between 12-week and delivery values in unsupplemented group was highly significant, $P<0\cdot001$). Umbilical venous values were higher than maternal delivery values in both groups.

During pregnancy total Ca concentration tended to increase in both groups with no correlation between ionised and total Ca except at delivery (maternal values positively correlated).

The percentage of ionised relative to total Ca decreased during pregnancy, being significant in the unsupplemented group (39·5 to 31·8%; $P<0\cdot001$).

Ionised Ca does not have a constant relationship to total Ca during pregnancy.

An enzymic polarographic sensor for continuous measurement of glucose concentration *in vivo*. R. M. Gardiner and I. A. Silver. Physiological Laboratory, Cambridge, and Department of Pathology, University of Bristol Medical School, Bristol.

The hydrogen peroxide generated as glucose reacts with oxygen in the presence of glucose oxidase can be measured at a platinum anode, and a glucose sensor based on this principle has been described (Clark and Clark, 1973). A modification of the Clark glucose electrode has been designed which is small enough for intravascular use.

A 1·0 mm length of Teflon-coated platinum iridium alloy wire (bare diameter 175 µm) is stripped of Teflon, lightly platinised, and dipped into an aqueous solution of catalase-free glucose oxidase. The active tip is subsequently treated in cold 1% glutaraldehyde, and a membrane applied by dipping in cellulose di-acetate. The electrode is maintained at a potential of +700 mV with respect to a sintered silver–silver chloride reference electrode.

Its characteristics have been investigated *in vitro* during immersion in well-stirred plasma at 38°C. Response times (95% of step change) range from 6 to 30 seconds depending on membrane thickness, and the response is linear within the physiological range of glucose concentrations (1–10 mmol/l). Recordings have been made *in vivo* of the changes in blood glucose concentration which follow administration of insulin, adrenaline, and glucose in the heparinised calf and lamb.

Reference

Clark, L. C., and Clark, E. W. (1973). Differential anodic enzymic polarography for the measurement of glucose. *Advances in Experimental Medicine and Biology*, **37A**, 127–133.

Sucking patterns of human babies at the breast. R. F. Drewett, A. Bowen-Jones, and M. Woolridge (introduced by J. D. Baum). Department of Psychology, University of Durham, and Department of Paediatrics, John Radcliffe Hospital, Oxford.

Studies of sucking patterns using bottles are of limited value in research on breast feeding, as they do not allow the sucking of the baby to be related to its natural consequence (the stimulation of the milk ejection reflex). We report an analysis of sucking on the breast made by filming the mouth of the baby.

Intersuck intervals fall on two distinct distributions, one of short intervals (<1·3 seconds) corresponding to the period of sucking, the other of longer intervals (>1·3 seconds) corresponding to pauses between bursts of sucking. The proportion of long intervals increases as the breast empties. In studies combining test weighing and sucking rate determinations the rate of sucking (within bursts) was found to increase as milk flow decreased.

These studies show, contrary to results derived from bottle feeding, that there is no simple dichotomy between 'nutritive' and 'non-nutritive' sucking, but rather that there is a single gradient of sucking rate of which these types represent the two extremes. The reflection of milk flow in the sucking pattern of the baby may be of use in clinical evaluation of breast-feeding difficulties.

Human milk cell concentration after storage in glass and plastic containers. C. Burns, D. M. Flynn, J. Kendra, and M. Szawatoski. The Royal Free Hospital, London.

Expressed breast milk is often stored without precautions being taken to conserve the cell content. Typically it is stored in glass vessels, although milk macrophages have been shown to have glass-adhesive properties (Smith and Goldman, 1968).

We investigated the concentration of human milk cells after storage in glass and polystyrene containers. 10 30-ml samples of milk were collected from nursing mothers. 10 ml of each sample was immediately examined for cellular concentration (control). 10 ml was stored in a glass test-tube and 10 ml in a polystyrene test-tube at 4°C for 8–16 hours before the cell concentration was established.

The mean cell count of the samples stored in polystyrene was 83% of the control, while the mean cell count of the samples stored in glass was 54% ($P<0·001$, paired *t* test). Differential cell counting showed that in the polystyrene-stored samples the proportion of macrophages and lymphocytes was greater than in the glass-stored samples; the reverse was true for the neutrophils. No tests were performed to assess the viability of the cells.

If human milk cells are considered of importance it is suggested that expressed breast milk be stored in polystyrene, or possibly other plastic containers, rather than in glass.

Reference

Smith, C. W., and Goldman, A. S. (1968). The cells of human colostrum. *In vitro* studies of morphology and functions. *Pediatric Research*, **2**, 103–109.

Use of doxapram in apnoea and hypoventilation in the neonate. J. E. H. Brice, A. W. Boon, and A. D. Milner. Department of Neonatal Medicine, City Hospital, Nottingham.

Three cases are reported in which doxapram was used to stimulate respiration in the neonate. The first two were very low birthweight, preterm infants with recurrent apnoea, not responding to oral theophylline and requiring assisted ventilation. The first had recurrent apnoea on withdrawing ventilation that was abolished for 15–25 minutes after each of 3 intravenous injections (0·5 mg) of doxapram. The second infant was given IV doxapram (1 mg bolus, followed by 0·5–1 mg/hour) to try to avoid a further period of assisted ventilation. A definite reduction in apnoea occurred but jittery movements were noted, probably related to the doxapram. The third case was a term infant with severe hypoventilation requiring assisted ventilation from the first day. All attempts to withdraw ventilation were unsuccessful until 5 days, when IV doxapram (5–10 mg bolus and hourly infusion) was administered with a striking improvement in spontaneous respiration. The doxapram was stopped two days later because of abnormal neurological signs, and the baby died.

These preliminary results suggest that doxapram is a more powerful respiratory stimulant than theophylline in the neonate and may have a place in the management of apnoea of prematurity. Little is known about the metabolism of doxapram, and possible side effects indicate that until further evaluated it should be used only when other established treatments have failed, and should be started in smaller doses than reported here.

An explanation for failure of impedance apnoea alarm systems. D. P. Southall, J. M. Richards, K. C. Lau, and E. A. Shinebourne. Department of Paediatrics, The Brompton Hospital, and Cardiothoracic Institute, London. To be published in full in the *Archives*, 1980, **55**, 63–65.

Daily changes in the curved crown-rump length of individual sheep fetuses during the last 60 days of pregnancy, and effects of different levels of maternal nutrition. D. J. Mellor. Moredun Research Institute, Edinburgh.

Archives of Disease in Childhood, 1979, **54**, 983–987

Correspondence

Comparison of IV salbutamol with IV aminophylline in severe acute asthma

Sir,

In a double-blind comparative study of children with acute asthma, Hambleton and Stone (*Archives*, 1979, **54**, 391) showed that IV salbutamol and aminophylline were equally effective when given during the first 24 hours.

The optimal use of theophylline requires a dosage regimen that maintains the serum concentration within the therapeutic range of 10–20 mg/l (Jenne *et al.*, 1972; Weinberger and Bronsky, 1974). Hambleton and Stone used a loading dose of 4 mg/kg followed by 0·6 mg/kg per hour. In a recent study (Selvig *et al.*, 1979), despite a bigger loading dose of 5 mg/kg in slightly older children (aged 8–15 years), therapeutic values were reached in only 62% of them and maximum serum concentration in each case was in the lower half of the range. A more suitable loading dose would have been 7·5 mg/kg, which is tolerated by most children, with average serum concentrations in the middle of the range (Weinberger, 1978). Furthermore, the infusion rate of 0·6 mg/kg per hour is much lower than the 0·85 mg/kg per hour recommended to maintain therapeutic serum concentrations in children less than 9 years (Hendeles and Weinberger, 1979).

The similar clinical effect shown by Hambleton and Stone when aminophylline dosage was subtherapeutic suggests to us that a different conclusion might have been reached had a therapeutic dose of aminophylline been used.

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Weinberger, M. M., and Bronsky, E. A. (1974). Evaluation of oral bronchodilator therapy in asthmatic children. *Journal of Pediatrics*, **84**, 421–427.

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Drs Hambleton and Stone comment:

We note the criticism about the dose of aminophylline and make the following comments. The assertion that therapeutic efficacy will be achieved when serum theophylline is 10–20 mg/l is based on the use of *oral* theophylline compounds in the prophylaxis of *perennial* asthma (Jenne *et al.*, 1972; Weinberger and Bronsky, 1974). Weinberger *et al.* (1976) gave data on *acute asthma* in children and evaluated the dosages necessary to maintain the above level. However, their paper did not indicate how effective their regimen was in terms of producing relief from asthma. Turner-Warwick (1957) studied acute wheezing in adults, and judged the appropriate serum levels simply from reports from patients on the subjective relief of symptoms after oral theophylline compounds. Selvig *et al.* (1979) studied serum theophylline levels after a single IV dose of aminophylline, and recommended a loading dose of 6 mg/kg but gave no information about maintenance treatment. Weinberger (1978) recommended a loading dose of aminophylline 5 mg/kg, and although he suggested 7·5 mg/kg in some children he pointed out that this dose would be toxic in others. Weinberger (1978) and Hendeles and Weinberger (1979) recommended 0·8 mg/kg per hour and 0·85 mg/kg per hour respectively as maintenance therapy, but gave no indication that these doses were necessary for relief of symptoms in *acute* asthma. They recommended that serial theophylline estimations should be carried out for patients individually, which is the ideal *modus operandi.*

In a double-blind trial such as ours, serum theophylline estimations during treatment are precluded. Pierson *et al.* (1974) used virtually the same dosage regimen as we did, and produced objective evidence that this was effective in acute asthma. In routine practice we have also found this regimen effective and so adopted it for the trial, being confident that there would be no side effects. It also facilitated the pharmaceutical preparation of our ampoules for the double-blind design, having regard to the dosage of salbutamol. We feel our results support those of Pierson *et al.* (1974) by providing objective evidence that this regimen is effective in acute asthma. The assertion that our dose of aminophylline is subtherapeutic is not justifiable. It is possible that a higher dose might have been more effective, but another double-blind trial would be necessary to establish this point.

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Lomotil in diarrhoeal illnesses

Sir,

The article by Curtis and Goel (*Archives*, 1979, **54**, 222) prompts me to place the usage of Lomotil in young children in the tropics in its right perspective. The problems of diarrhoea in the tropics are quite different when compared with temperate climates, and management of this condition is therefore also different.

In situations where children have little or no access to optimal therapeutic management, especially fluid therapy, symptomatic control of diarrhoea does become important and it is in this context that I find little objective evidence for Curtis and Goel to draw a general conclusion that the use of Lomotil is difficult to justify in children.

In their study only 6 of 45 patients had actually been prescribed Lomotil for a diarrhoeal illness, of which 4 took an accidental overdose. The remaining 39 children had ingested large quantities of the drug accidentally without any indication for its use, when adult relatives had been prescribed the drug. The authors state that no correlation was found between severity of symptoms and dose ingested, but the upper limits of dose range in their paper show that in the mild, moderate, and severe cases the quantity of drug ingested was 23 times, 33 times, and 40 times the therapeutically recommended dose.

Some time ago we were equally concerned about the use of Lomotil and so we conducted a dose response study in children suffering from nonspecific and specific diarrhoea (Karan *et al.*, 1976), using Lomotil in a dosage range of 0·2 to 0·3 mg/kg, and observed that the optimal dose for Indian children appears to be about 0·25 mg/kg. Furthermore, when used in this therapeutic dose there were no significant side effects or signs of toxicity, although children taking 0·3 mg/kg did have slightly more side effects, but these were not statistically significant.

I feel that Lomotil does have a role in managing diarrhoea in the tropics if used judiciously, but problems can arise if the correct dose is not given. Accidental overdosage can of course occur with any drug.

References

Karan, S., Vijaylakshmi, and Mukherjee, L. (1976). Assessment of safety of Lomotil in infants. *Indian Pediatrics*, **13**, 295–300.

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Sir,

This letter is in response to the paper by Curtis and Goel (*Archives*, 1979, **54**, 222). While I agree that there is a need to monitor Lomotil therapy in young children closely, our experience with this drug in this country does not justify their conclusions.

Curtis and Goel state that in only 13% (6 out of 45) cases was Lomotil actually prescribed for a diarrhoeal illness, and in the remaining 87% a large quantity of the drug was ingested by small children, where the drug was not prescribed primarily for them. Even in the former group, 4 of the 6 cases had an accidental overdose.

Bovier-Lapierre *et al.* (1973), Scorza *et al.* (1974), and Wasserman (*Journal of the American Medical Association*, 1974) clearly differentiate the incidence of intolerance and intoxication. Although the former can occur with lower doses in children who are hypersensitive to the drug, the total incidence of such effects is relatively low compared with the intoxication effects seen after accidental ingestion of large doses and this is very much a dose-related effect. It surprises me that Curtis and Goel do not think this is so, because the upper limits of the dosage range in their own data are 5·8, 8·4, and 10 mg/kg respectively, in the mild, moderate, and severe cases, compared with the therapeutic dose of 0·25 mg/kg.

Morbidity and mortality from diarrhoea in the tropics is such that rapid control of diarrhoeal symptoms becomes mandatory and the rationale of management becomes slightly different from the one seen in other parts of the world. It is in such a setting that we evaluated the role of Lomotil in diarrhoea in children below 2 years (Limaye, 1979); we found that the judicious use of this drug did not result in any undue toxicity.

Lomotil is certainly no panacea for diarrhoea but it does offer the paediatrician, at least in the tropics, a useful mode of speedy correction of diarrhoeal symptoms. However, we agree with Curtis and Goel that when prescribed for adult relatives, the drug should be kept out of reach of children.

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Dr Goel comments:

It was certainly not our intention to exclude the use of Lomotil as an antidiarrhoeal agent in children in the tropics. No doubt all who treat such children would agree that the mainstay of treatment of diarrhoea in children in any part of the world is the correction of fluid, electrolyte, and acid-base status, and not the reduction of intestinal motility by an antidiarrhoeal agent. If, as suggested by Dr Karan, such therapeutic measures are not available, then perhaps one could use an antidiarrhoeal drug, such as Lomotil, though only with caution. This is because, in our experience, it is not possible to predict what dose will be toxic in children.

Both Dr Karan and Dr Limaye emphasise that in our cases severity of the symptoms was related to the dose ingested, and they also imply that symptoms only occur above a recommended therapeutic dose 0·25 mg/kg a day. But they fail to observe that on the contrary the figures for the lower limit of the ingested dose (mild, 0·62 mg/kg; moderate, 0·25 mg/kg; and severe, 0·77 mg/kg) did not correlate with the severity of symptoms. We suggest that if it is necessary to use Lomotil the prescribing doctor should take cognisance of the risks.

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Infantile cortical hyperostosis with raised immunoglobulins

Sir,

Ramchander and Ramkissoon (*Archives*, 1978, **53**, 426) drew attention to the IgA and IgM levels in 2 cases of infantile cortical hyperostosis (Roske-de Toni-Caffey syndrome). They said that a virus infection during intrauterine or neonatal life might be the cause of this disorder.

I know 2 Italian families in which this disease was diagnosed in two generations: in the first family, in the mother and her son; in the other family, the father, the daughter, and the father's first-cousin all had the disease (Duillo and Cerruti Mainardi, 1969). A few months ago another girl was born in the second family, and she shows the same disorder at age 8 weeks.

These cases, as do many other familial ones in the literature, support de Toni's hypothesis (de Toni, 1943) that genetic factors may play a rolè in the aetiology of this mysterious disease.

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Polyarthritis associated with Wilson's disease

Sir,

A 14-year-old boy was admitted to hospital in August 1978 with an acute attack of polyarthritis which he had had for one day, and which affected both knees and elbows. There was no history of sore throat, and the family history was unremarkable. On examination he was pale, and the affected joints showed effusion with tenderness and heat. Small spider telangiectases were present over the upper sternum, and both spleen and liver were slightly enlarged. Slit-lamp examination showed Kayser Fleischer rings in both corneae.

Full blood picture, ESR, urine analysis, liver function tests, ECG, serum urate, Hb electrophoresis, C-reactive protein, latex-fixation test, throat swab culture, lupus erythematosus phenomenon, were all negative. ASO titre, 333 IU/ml. Percutaneous liver needle biospy showed fatty changes. Serum copper 77·96 μg/100 ml (12 μmol/l), serum caeruloplasmin 105 mg/l (10·5 mg/100 ml), urinary copper 261 μg/24h (4·09 μmol/24h).

The boy subsequently developed two further attacks of polyarthritis during the next 2 months; the findings and investigations then were similar with ASO titre 166 and 250 IU/ml.

He responded well to paracetamol initially, and was then put on D-penicillamine, when he remained well until last seen in June 1979.

The association of polyarthritis with Wilson's disease has not been previously reported, and may have been coincidental, but slit-lamp examination of atypical cases of arthritis in children would be prudent.

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Sodium valproate, pregnancy, and neonatal hyperglycinaemia

Sir,

It has been demonstrated that sodium valproate (SV) crosses the placenta freely and that maternal serum levels will reflect fetal serum levels (*Archives*, 1979, **54**, 240). The SV concentration in the serum of a neonate was of the same order as that of the mother's at delivery, but fell to insignificant levels by 5 days and was undetectable at 29 days. As this child appeared healthy, it was concluded that the use of SV in pregnancy was safe.

On the other hand, administration of SV is known to cause hyperglycinaemia and hyperglycinuria in patients suffering from epilepsy (Jaeken *et al.*, 1977; Kamoun and Parvy, 1978; Similä *et al.*, 1979). In experiments on animals it has been shown that the rate of influx of glycine and other amino-acids into the brain is higher in the newborn period than later in life (Seta *et al.*, 1972; Banos *et al.*, 1978). In addition, high concentrations of glycine, which are found in nonketotic hyperglycinaemia and many organic acidaemias, are associated with severe impairment of neuronal function, and therefore a high plasma level of glycine during early postnatal life may be a risk factor (Tanaka, 1975; von Wendt *et al.*, 1978). Therefore, we monitored the clinical state and the levels of plasma glycine and serum SV postnatally in 2 neonates; in both, the mothers had received SV treatment during pregnancy.

Case 1

A 25-year-old woman, II para, in whom epilepsy had been diagnosed in 1972, had taken SV since March 1977. Throughout the pregnancy her dosage was SV 1350 mg/day and phenytoin 450 mg/day divided in 3 doses.

In spite of therapeutic serum concentrations of these two drugs, she had had several major convulsions during early pregnancy. Delivery took place at term, the healthy boy (weight 3440 g, Apgar score 9/10) did not show any abnormalities; growth and development during the first year of life were normal as was the EEG.

Case 2

A 24-year-old woman, III para, who had suffered from epilepsy since 1968, was started on SV in January 1978 (4 months before conception). During pregnancy she was well controlled taking SV 1200 mg/day, phenytoin 400 mg/day, carbamazepine 600 mg/day, and clonazepam 1 mg/day. A healthy girl, weighing 4000 g was born at term. The Apgar score was 9/9, the initial EEG and development during the first 2 months were normal.

The serum level of SV was measured in the mothers at delivery and in the neonates at birth and repeatedly postnatally. At birth, SV levels were 220 and 110 µmol/l in the neonates, and 200 and 210 µmol/l in the mothers, but fell to insignificant concentrations by 5 days and were undetectable at 9 days (Figure).

The plasma concentration of glycine rose markedly during the first postnatal day, the highest levels being 665 and 605 µmol/l. These values differed very significantly from controls (Figure).

From these 2 case histories it is concluded that the use of SV in the last trimester of pregnancy induces a transient secondary hyperglycinaemia in the neonatal period, although the plasma glycine concentrations are clearly lower than in nonketotic hyperglycinaemia or organic acidaemia associated with hyperglycinaemia (Tanaka, 1975; von Wendt *et al.*, 1978). As these infants show normal psychomotor development, it is evident that this moderate rise of glycine concentration does not impair the development of the CNS. However, it should be borne in mind that treatment with SV during pregnancy can cause a false-positive finding in metabolic screening for aminoacidaemias in newborn babies.

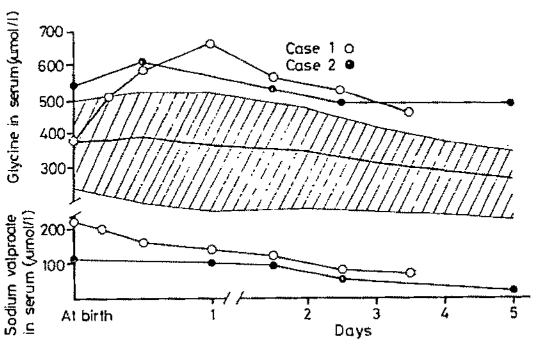

Figure *Glycine* (*upper part*) *and sodium valproate* (*lower part*) *in plasma and serum respectively in 2 newborn babies during the first 5 postnatal days. Normal range of postnatal glycine levels in plasma* (*mean* ± *SD, n* = *10*) *is shown by shaded area.*

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Neutropenia during sodium valproate treatment

Sir,

Thrombocytopenia is a well-known side effect of sodium valproate (dipropylacetic acid) treatment (Winfield *et al.*, 1976; Raworth and Birchall, 1978; Sandler *et al.*, 1978). As far as we know, neutropenia has not been documented during valproate medication. Recently we treated a 3-month-old boy with sodium valproate (40 mg/kg per day) because of postanoxaemic convulsions. No other drugs were given. Total blood neutrophils decreased steadily from pretreatment values between 3·5 and 5·4 × 10^9/l to a value as low as 0·460 × 10^9/l during the next 2 months. Valproate was stopped and total neutrophil count promptly increased to 2·0 × 10^9/l within 14 days and to pretreatment values within a few weeks. Thrombocytes remained within normal limits. Erythrocyte count did not change. Because of the fragile condition of the infant a bone marrow puncture was not performed. Antibodies against thrombocytes have been shown in valproate-induced thrombocytopenia (Sandler *et al.*, 1978); in our patient immunofluorescence studies at the time of the lowest neutrophil count failed to demonstrate antibodies against granulocytes. Thrombocytopenia, and now neutropenia, as well as hyperglycinaemia (Jaeken *et al.*, 1977; Kamoun *et al.*, 1977), normal glycinorrhachia (Jaeken *et al.*, 1977), and ketonuria (Simon and Penry, 1975), all reported in association with sodium valproate medication, are classical findings in ketotic hyperglycinaemia (Scriver and Rosenberg, 1793). This suggests that sodium valproate can induce a biochemical syndrome similar to that of the ketotic hyperglycinaemias.

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Book reviews

Clinical Pharmacology and Therapeutics: A Pediatric Perspective. Edited by Bernard L. Mirkin. (Pp. 339; illustrated + tables. £24.50 hardback.) YB Medical Publishers: Chicago. 1978.

After many teething difficulties, paediatric clinical pharmacology has come of age and a rapidly expanding data base resulting from excellent paediatric studies bears testimony to this fact. This book, based on a conference proceedings, and consisting of papers contributed by many of the foremost authorities on paediatric pharmacology, aims to identify the origins and nature of the available information, and to present it in such a way as to facilitate a rational approach to paediatric therapeutics.

It looks at five major areas of knowledge and concern. A discussion of factors modulating drug action in immature organisms provides an introduction to the second part which describes pharmacokinetic principles and their application to drug use, with particular reference to anticonvulsants and digoxin. The third section thoughtfully explores drug therapy in malignancy and virus diseases, and the more topical subjects of drug effects on lung maturation and the patent ductus arteriosus. Other problems of pre- and early postnatal drug therapy, the emotional disorders, and pharmacology of antihypertensive agents are clearly reviewed in the fourth part, and an excellent discussion on the general ethical principles governing drug research and investigation in children is included in the final section, which is mainly concerned with drug regulations more applicable to the USA.

The book, which makes no claim to being a comprehensive handbook of paediatric pharmacology, is a good one, and because of its nature, cannot be criticised for omissions. Its aims have been clearly achieved and there are no noticeable errors or unjustified statements. Readers looking for information on the treatment of specific paediatric problems will be disappointed, although they will not fail to recognise the principles on which a paediatric pharmacological approach is based and which are so firmly adhered to by the contributors. The paper on anticonvulsants by Morselli and Baruzzi particularly emphasises these principles by its numerous omissions of pharmacokinetic parameter values for almost half the drugs and age groups considered. Not for these authors the substitution of adult values for those of children, but rather an earnest plea for more data.

Paediatricians, who believe that the 'children are not small adults' maxim extends to drug use, will find much to interest them in this book.

GEORGE RYLANCE

Metabolic Disease in Childhood. By Leonard Sinclair. (Pp. 566; illustrated + tables. £27.50 hardback.) Blackwell: Oxford. 1979.

This book covers clinical, genetic, molecular, and therapeutic aspects of the great majority of metabolic disease in childhood. It is divided in three sections. The first deals with general topics—such as incidences, screening, genetic principles, and basic enzymology. The second section deals with symptomatology and common metabolic problems in paediatric practice. In the third and largest section, metabolic disorders are considered systematically and classified under the headings of disorders of active transport, disorders characterised by excessive storage or accumulation, disorders of intermediary metabolism, and disorders of synthesis. This logical classification of inborn errors of metabolism will help newcomers to the field in understanding the numerous and diverse consequences of disordered phenotypic expression of genetic enzyme defects. Further ramifications of the proposed reclassification are generally equally logical. However, the advantages of classifying Niemann-Pick disease and metachromatic leucodystrophy as examples of globosidosis (rather than of sphingolipidosis) are not evident, since the metabolic block in these disorders is in the removal of residues (phosphorylcholine, sulphate) which are not present in globoside. A number of slips (for example, induronidase, β-mamnosidase, Tay-Sachs gene in 1 in 1000 Ashkenazis) require correction in the next edition.

The easily readable, comprehe descriptions of these complicated often extremely rare disorders will b great value to clinicians, biochemists, others involved in the care of children v metabolic disorders.

P. F. BENS

Pediatric Cancer Chemotherapy. By R. A. Al-Rashid. (Pp. 319; illustrated + tables. £10.25 paperback.) Kimpton: London. 1979.

This soft-backed book provides a synopsis of the current state of the practice of paediatric cancer chemotherapy. The author, who is Director of the Pediatric Hematology and Oncology Service in the University of Nebraska College of Medicine, points out that because of continuing development in the field it is impossible to cover all aspects of drug therapy in malignant disease, and that treatment programmes for one tumour may vary from one centre to another. His aim is to provide a framework of information to enable clinicians in the field to understand the basis for the treatments. The first two chapters cover the clinical pharmacology of the anticancer drugs and the principles of cellular kinetics and chemotherapeutic strategy. The next 10 chapters cover the chemotherapy of the major paediatric malignancies, and the final one the late effects of cancer chemotherapy. The chapters dealing with specific disorders are subdivided into sections setting out the background development, discussion of different established regimens, and the treatment of recurrent disease.

This book suffers from the rather artificial division of chemotherapy from other modalities of management and could not be used to plan a whole treatment programme. In general, however, it provides an excellent reference to modern paediatric cancer chemotherapy in an easily readable and transportable form. It has an extensive bibliography, although references more recent than 1976 are rare.

P. H. MORRIS JONES

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R. S. Gibson and M. S. DeWolfe (Halifax, Nova Scotia, Canada)

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P. Wieland, G. Duc, J. A. Fischer, and U. Binswanger (Zurich, Switzerland)

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